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Progressive Dwindling in Multiple Sclerosis: An Opportunity to Improve Care

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Keywords:	Multiple sclerosis; formative care; trajectory to death
Abstract:	Introduction: In the general ageing population, 40% of deaths occur following a prolonged trajectory of 'progressive dwindling', characterised by chronic accumulation of disability and frailty, and associated with increased dependency and reduced reserves. Those who progressively dwindle are poorly catered for by current healthcare systems and would benefit from a coordinated approach to their medical and social care, known as formative care. People with multiple sclerosis (pwMS) may be more likely to progressively dwindle, and may be appropriate targets for formative care pathways. Objectives: To determine the proportion of pwMS who follow a progressive dwindling trajectory prior to death. To relate trajectory to place of death, and examine what factors predict the progressively dwindling trajectory. Methods: A retrospective observational study of 582 deceased pwMS enrolled in the UK MS Tissue Bank, including death certificates and extensive clinical summaries. Results: 73.7% of pwMS had a 'progressively dwindling' trajectory of dying. This was predicted by those who reach MS disease milestones earlier. 72.5% of pwMS died an MS-related death, which was predicted by an aggressive disease course from onset. Those who progressively dwindled were equally likely to die in hospital as those with other trajectories to death. Conclusions: The progressively dwindling trajectory of dying is very common in pwMS, and can be predicted by earlier disease milestones. Pathways could target pwMS in these years prior to death, to improve care.
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Ethics Statement	The UKMSTB has ethical approval from the London Multicenter Research Ethics

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Please describe where your data may be found, writing in full sentences. **Your answers should be entered into the box below and will be published in the form you provide them, if your manuscript is accepted.** If you are copying our sample text below, please ensure you replace any instances of XXX with the appropriate details.	Raw data has not been provided as it contains patient identifiable information, and is custody of the UK MS Tissue Bank. Requests for data can be made to the UK MS Tissue Bank via Dr Richard Nicholas (r.nicholas@imperial.ac.uk).

If your data are all contained within the paper and/or Supporting Information files, please state this in your answer below. For example, “All relevant data are within the paper and its Supporting Information files.” If your data are held or will be held in a public repository, include URLs, accession numbers or DOIs. For example, “All XXX files are available from the XXX database (accession number(s) XXX, XXX)." If this information will only be available after acceptance, please indicate this by ticking the box below. If neither of these applies but you are able to provide details of access elsewhere, with or without limitations, please do so in the box below. For example: “Data are available from the XXX Institutional Data Access / Ethics Committee for researchers who meet the criteria for access to confidential data.” “Data are from the XXX study whose authors may be contacted at XXX.” * typeset	
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Cover Letter

Dear Editor and Reviewers,

We are very grateful for the reviewers' comments regarding the manuscript "Progressive Dwindling in Multiple Sclerosis: An Opportunity to Improve Care". We believe that all reviewer comments have now been addressed, and the manuscript is much improved as a result. Please find attached a clean version of the revised manuscript, and a manuscript with 'track changes'. In addition, we have addressed each reviewer comment in the 'response to reviewers' document.

Addendum 1.6.16: After submission of this revision, we received an email from Samantha Russell (24/5/16) of PLOS ONE to clarify three points:

1. *Raw data has not been provided as it contains patient identifiable information, and is custody of the UK MS Tissue Bank. Requests for data can be made to the UK MS Tissue Bank via Dr Richard Nicholas (r.nicholas@imperial.ac.uk). Samantha Russell has kindly offered to amend our data availability statement on our behalf.*
2. *Funding information has been removed from the acknowledgements sections, as advised. Please can you add to the Funding Statement: "Dr Richard Nicholas is supported by the National Institute for Health Research."*
3. *As requested, we have made it clearer that all author are affiliated to Imperial College London by adding superscript numbers beside each author.*

We thank the editor and the reviewers for their time, and for considering this manuscript.

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Progressive Dwindling in Multiple Sclerosis: An Opportunity to Improve Care

Short title: Progressive Dwindling in Multiple Sclerosis

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Key words: Multiple sclerosis, formative care, trajectory to death

Abstract

Introduction: In the general ageing population, 40% of deaths occur following a prolonged trajectory of 'progressive dwindling', characterised by chronic accumulation of disability and frailty, and associated with increased dependency and reduced reserves. Those who progressively dwindle are poorly catered for by current healthcare systems and would benefit from a coordinated approach to their medical and social care, known as formative care. People with multiple sclerosis (pwMS) may be more likely to progressively dwindle, and may be appropriate targets for formative care pathways.

Objectives: To determine the proportion of pwMS who follow a progressive dwindling trajectory prior to death. To relate trajectory to place of death, and examine what factors predict the progressively dwindling trajectory.

Methods: A retrospective observational study of 582 deceased pwMS enrolled in the UK MS Tissue Bank, including death certificates and extensive clinical summaries.

Results: 73.7% of pwMS had a 'progressively dwindling' trajectory of dying. This was predicted by those who reach MS disease milestones earlier. 72.5% of pwMS died an MS-related death, which was predicted by an aggressive disease course from onset. Those who progressively dwindled were equally likely to die in hospital as those with other trajectories to death.

Conclusions: The progressively dwindling trajectory of dying is very common in pwMS, and can be predicted by earlier disease milestones. Pathways could target pwMS in these years prior to death, to improve care.

Introduction

Over the last century there has been a shift in the commonest causes of death, from acute causes at a young age, to a substantially lengthened lifespan characterised by a period of progressive chronic illness before death.[1] Bowman and Meyer (2014) described four broad trajectories of dying in an ageing population:[2]

- 20% are sudden e.g. myocardial infarction;
- 20% of deaths follow a short period of rapid decline after a 'clear clinical transition' from treatable to progressive e.g. cancer;
- 20% occur as a result of acute exacerbations of a progressive long-term disease e.g. chronic obstructive pulmonary disease;
- 40% of deaths occur following a prolonged period of 'progressive dwindling' e.g. Alzheimer's disease.

For the first three trajectories, healthcare infrastructure is well established and effective, with preventative and emergency medicine for the sudden trajectory, palliative care for those with a short period of rapid decline, and specialist chronic disease management programmes for those with progressive long-term diseases with acute exacerbations.[2] However, there is a lack of appropriate pathways for those who 'progressively dwindle', with often haphazard involvement of a wide range of healthcare professionals and services, and thus care can be sub-optimal.[2] A report from the UK Parliamentary and Health Service Ombudsman in May 2015 found a lack of coordination of care services, delays in referral and inadequate out-of-hours services have led to poor end of life care for a large number of patients.[3] The report suggested this could be improved by proper service delivery and organisation.[3] The term 'formative care' has been coined to describe the strategy of "enabling the best possible life quality and experience in the context of a life

reframed by frailty and dependency" for progressively dwindling patients in the time between active treatment and end of life care.[2] Aspects of formative care overlap with palliative care, including symptom relief and home care, although formative care focuses on maximising quality of life rather than quality of death, and takes place over years rather than weeks or months. Elements of formative care might include access to regular tailored physiotherapy, occupational therapy visits to the home environment, nutritional support, pathways to determine when packages of care should be escalated and improving this transition, and rationalising medication, focusing on those that improve quality of life. Promoting implementation of formative care from an early stage will also allow improved transition into palliative care, and act as a buffer against difficulties in determining when palliative care should begin. Identifying markers to predict those who will adopt a progressive dwindling trajectory will be essential for implementing formative care in a timely manner for these patients.

People with MS (pwMS) have a prolonged disease course, often 50 years or more.[4] Disease modifying therapies are available for relapsing MS, but there are currently no licensed treatments for the progressive phase. As a result, a gap in structured care pathways has arisen between active treatment and end of life care, in which pwMS may spend a prolonged period 'progressively dwindling', with considerable distress associated with decline in physical and mental function.[5] This period without active treatment but before palliation is not specific to MS, but is particularly pertinent due to the extended and unpredictable timeframe. It is during this phase that pwMS could greatly benefit from formative care. Those pwMS who progressively dwindle experience a slow and steady accumulation of disability,

resulting in frailty, and associated with increased dependency and reduced physiologic reserve.[6] This period extends for many years before death, during which time there is an increasing burden of care, often taken on by the family, and punctuated by superimposed illness. As the ever-reducing physiologic reserve resets the baseline, there is reduced capacity to cope with said periods of superimposed illness, such as pneumonia, and ultimately these present the terminal event.[6] Because formative care promotes adequate planning of and improved transition to palliative care due to overlap in techniques, it should also empower patients to choose to die at home, if this is their wish. To understand how formative care might help pwMS, this study aimed to: (i) determine the frequency of progressive dwindling in an MS population, (ii) identify factors associated with progressive dwindling, (iii) determine specific cause of death and whether deaths were ultimately MS-related or not, and (iv) examine place of death in those with different trajectories to death.

Materials and Methods

Data collection

Data were retrospectively collated from a cohort of 582 pwMS who had died between January 1998 and February 2015 inclusive, and had been registered on the UK MS Tissue Bank (UKMSTB). The UKMSTB is a national scheme to collect post-mortem tissue donated from pwMS and non-MS controls, as well as death certificate data, clinical summaries and extensive clinical notes. As of February 2015, the UKMSTB stored post-mortem data on 606 pwMS; all were included in this study after exclusion of 9 donors without a confirmed tissue diagnosis of MS, and 15 donors with insufficient data on cause of death. Clinical notes were used to define the date of symptom onset, progressive disease (defined as a period of at least one year with gradual disability worsening without relapses), wheelchair use, and death, for all patients. Participants with missing data on symptom onset, progression, wheelchair use, and/or place of death were included in the study, but were excluded from relevant analyses. The UKMSTB has ethical approval from the London Multicenter Research Ethics Committee (MREC/02/2/39) to prospectively recruit donors after obtaining written informed consent, and accrue an extensive clinical summary from medical notes and death certificates as previously described.[7]

Classification of death: Cause, MS-related, Trajectory, and Place

Death certificate entries were used to categorise underlying cause of death (UCD), and confirmed using patient notes and clinical summaries when the death certificate was unclear. For example, if the death certificate stated ‘infection’ or ‘respiratory failure’, clinical notes were used to identify a more specific UCD e.g. pneumonia. If multiple causes were listed on the death certificate, clinical notes were used to

discern the primary cause of death. If multiple causes of death were listed, the diagnosis that triggered the chain of events leading to death was chosen (e.g. pneumonia leading to respiratory failure). Where it could not be discerned whether one was more responsible that the other (e.g. pneumonia and UTI), and the clinical notes did not clarify, the first listed was used as the UCD. UCD was only categorised as MS when no other cause was listed; where possible a more specific cause (e.g. pneumonia) was used, even if secondary to MS. Deaths were also classified as being 'related to MS' or not, by examining death certificates and clinical notes. Trajectory to death categories were adapted from Bowman and Meyer;[2] trajectory was based on cause of death and review of the clinical summaries. Place of death categories were based on Public Health England's place of death classification.[8] Own residence, care home and hospice deaths were also combined into a 'community' category.

Statistical analysis

Cox proportional hazards regression was performed to compare survival from disease milestones between different groups e.g. those with MS-related deaths vs. those with non-MS-related deaths, those who progressively dwindled vs. those with other disease trajectories. Disease milestones were compared between all four disease trajectory groups using one way between subject ANOVA, with Tukey HSD used post hoc for significant ANOVA analyses. Student's t-test was used to compare demographics in males and females. Parametric tests were performed after testing for normality. Chi-squared test was used to compare location of death in those with different trajectories to death, and those with and without MS-related deaths. Yates' chi-squared test was used to avoid overestimation of statistical significance. Where

chi-squared revealed significance in contingency tables greater than 2x2, further post hoc 2x2 chi-squared tests were carried out to identify the significant values, with criteria for statistical significance adjusted according to the number of post hoc tests carried out.

Results

Study population and cause of death

582 deceased pwMS were included in the analysis. 70% were female, and the average age at symptom onset was later among females than males (34.1±10.7 [mean±SD] vs 30.6±9.7 p<0.001). The average age of progression was 45.5±11.3, the average age of wheelchair use was 50.6±12.8 and the average age at death was 63.8±12.7 years with women dying later than men (64.9±13.1 vs 61.2±11.5, p<0.01). 68.5% were categorised as secondary progressive MS at the time of death, 11.4% primary progressive, 6.0% relapsing remitting, and the sub-type of MS was unavailable in 14.1%. The most common UCD was pneumonia or bronchopneumonia (37.5%), followed by MS (14.8%), cancer (10.1%), and aspiration pneumonia (8.6%; Table 1). 72.5% died an MS-related death. 35.9% of pwMS did not have MS recorded on any part of their death certificate; including 28.7% of those whose death was adjudged to be MS-related after inspection of clinical notes in this study.

Table 1. **Cause of death of 582 people with MS, UKMSTB January 1998 to February 2015.**

Cause of death specific categories	**n (%)**
Multiple sclerosis	86 (14.8)
Pneumonia, bronchopneumonia	218 (37.5)
Aspiration pneumonia	50 (8.6)
Urinary tract infection	34 (5.8)

Other infection, inc. sepsis	12 (2.1)
Acute cardiovascular event	22 (3.8)
Acute cerebrovascular event	18 (3.1)
Pulmonary embolism	14 (2.4)
Non-acute cardiac e.g. senile myocardium or heart failure	11 (1.9)
Respiratory failure	9 (1.5)
Infection secondary to chronic obstructive pulmonary disease	7 (1.2)
Cancer	59 (10.1)
Acute abdomen e.g. obstruction	13 (2.2)
Suicide	7 (1.2)
Epilepsy	3 (0.5)
Other e.g. fulminant liver failure, renal failure, dehydration, acute pyelonephritis, tuberculosis, old age, myelodysplastic syndrome, liver abscess, progressive multifocal leukoencephalopathy, general deterioration, anaphylactic reaction, cardiac asthenia amyloid, ruptured left subclavian artery aneurysm, necrotic fasciitis, accidents, dementia, and frailty.	19 (3.1)

MS-related deaths are predicted by markers of aggressive disease

Of the 582 pwMS, 72.5% died an MS-related death. MS-related deaths were associated with younger age at symptom onset (MS-related: 31.6±9.9; non MS-

related 36.9±10.9, p<0.0001), progression (MS-related: 43.5±10.3; non MS-related 51.3±11.9, p<0.0001), wheelchair use (MS-related: 48.4±11.9; non MS-related 57.6±12.9, p<0.0001) and death (MS-related: 61.5±12.4; non MS-related 68.9±11.6, p<0.0001). MS-related deaths were also associated with a shorter time from symptom onset to death (MS-related: 29.4 ±11.9; non MS-related 32.9±12.7, p<0.01). These earlier milestones are indicative of more aggressive disease courses leading to MS-related deaths (Figure 1).

Figure 1. Cox proportional hazard regression model comparing disease length leading to MS-related deaths and unrelated deaths.

Those whose death was MS-related had a shorter disease course from symptom onset to death than those whose death was unrelated (R^2=0.016, n=504, p<0.01; MS death 1.32, 95CI 1.08-1.61). Dotted line represents MS-related deaths; solid line represents non-MS-related deaths.

Progressive dwindling is a common trajectory in MS, and is predicted by earlier disease milestones

Of 582 pwMS, 429 (73.7%) progressively dwindled, 76 died a sudden death, 59 experienced a clear clinical transition from a treatable to an unrelenting progressive disease (e.g. cancer), and 18 died as a result of an acute exacerbation of a progressive long-term condition. When comparing those who progressively dwindled with the other trajectories combined, those who progressively dwindled had earlier age at onset, progression, wheelchair use and death (all p<0.01; Figure 2). Differences between groups remained when comparing individual groups in a one-

way between subjects ANOVA (Table 2). More specifically, after post-hoc Tukey HSD, those who progressively dwindled had a mean age at MS onset five years earlier than those who died suddenly ($p<0.01$). Those who experienced a progressive dwindling trajectory had an earlier age at progression than those who died following a clear clinical transition ($p<0.05$) or an acute exacerbation ($p<0.01$). Those who experienced a progressive dwindling course were wheelchair-bound 9 years earlier than those who died following acute exacerbations and 5 years earlier than those who died suddenly (both $p<0.05$). Those who progressively dwindled died at a younger age than those who experienced any other trajectory to death (all $p<0.05$). There was no significant relationship between the trajectory to death and interval from symptom onset to death.

Figure 2. Cox proportional hazard regression models of disease milestones in those who progressively dwindle compared to other trajectories.

Those who progressively dwindle had an earlier age at onset (A, $R^2=0.02$, n=504, p<0.01; Progressive dwindling: 1.08, 95CI 1.03-1.14), progression (B, $R^2=0.024$, n=390, p<0.01; Progressive dwindling :1.09, 95CI 1.03-1.16), wheelchair use (C, $R^2=0.022$, n=462, p<0.01; Progressive dwindling: 1.09, 95CI 1.03-1.15) and death (D, $R^2=0.014$, n=582, p<0.01; Progressive dwindling: 1.07, 95CI 1.02-1.12). Dotted lines represent those with progressive dwindling trajectory to death; solid line represents all other disease trajectories.

Table 2. Different Trajectories association with MS milestones.

Trajectories	Mean age at symptom onset ±SD (n)	Mean age at progression ±SD (n)	Mean age at wheelchair ±SD (n)	Mean age at death ±SD (n)
Clear clinical transition	35.3±10.0 (54)	50.2 ±9.9 (38)	54.2±10.6 (39)	67.7±10.2 (59)
Acute exacerbation of progressive long-term condition	35.5±10.4 (15)	54.5±15.3 (12)	58.5±13.6 (13)	71.2±9.2 (18)
Sudden	36.9±10.7 (65)	47.1±10.4 (42)	54.4±13.0 (56)	66.5±12.1 (76)
Progressive dwindling	32.0±10.3 (370)	44.3±11.1 (298)	49.3±12.6 (354)	62.5±13.0 (429)
ANOVA Significance	p<0.01	p<0.001	p<0.001	p<0.001

The significant associations as identified by post-hoc Tukey HSD are detailed under ‘Progressive dwindling is a common trajectory in MS, and is predicted by earlier disease milestones’.

Location of death

Of 582 donors included in the study, place of death was available for 503 donors (86.4%). Of those, 50.7% died in hospital, 25.4% died in a care home, 18.9% died in their own residence, 4.6% died in a hospice and 2 died in other locations. Those who progressively dwindled were equally likely to die in hospital as those with other trajectories to death (Table 3).

Table 3. Community vs. hospital and trajectory to death

	Community n (%)	**Hospital n (%)**	**Total**
1 Clear clinical transition	33 (61.1)	21 (38.9)	54
2 Acute exacerbations of progressive long-term conditions	3 (23.1)	10 (76.9)	13
3 Sudden	32 (47.8)	35 (52.2)	67
4 Progressive dwindling	178 (48.5)	189 (51.5)	367
Total	246 (49.1)	255 (50.9)	501

NB: two died in 'other' locations which were not classified into community or hospital.
Own residence, care home and hospice deaths were combined into a 'community' category.

Similarly, those whose death was MS-related were equally likely to die in hospital as those whose death was unrelated to MS (Table 4). Those with MS-related deaths were less likely to die in a hospice – a category dominated by those with cancer-related deaths. Dying in the community rather than in hospital was not associated with an earlier death or a shorter interval from symptom onset to death.

Table 4. The relationship between place of death and whether a death was MS-related.

Significantly lower numbers of subjects died an MS-related death in hospices compared to those who had a non MS-related death ($p<0.01$, χ^2 test).

	MS-related death n (%)	**Not MS-related death n (%)**
1 Own residence	67 (70.5)	28 (29.5)
2 Hospital	184 (72.2)	71 (27.8)
3 Care homes	98 (76.6)	30 (23.4)
4 Hospice	9 (39.1)	14 (60.9)
5 Other†	0	2
Total	358 (71.2)	145 (28.8)

† excluded from χ^2 test

Discussion

This study finds rates of progressive dwindling in pwMS far greater than in the general population. These results emphasise the extended and unpredictable timeframe between active treatment and end of life care in MS, and the high proportion of pwMS who have prolonged periods of frailty, dependency, and reduced physiological reserve for many years prior to death. Those who progressively dwindle are equally likely to die in hospital as those with more acute trajectories to death, which might be interpreted as a failure of care. This study also finds that progressive dwindling can be predicted by early markers of aggressive disease in pwMS, suggesting an opportunity for targeted formative care in this subset of patients.

The UKMSTB is a community based scheme where people with MS register during their lifetime for tissue and clinical data to be collected when they die. Donors are representative of MS patients nationwide as a result of a national community-based recruitment strategy, with accurate representation of clinical milestones and MS sub-types confirmed by comparison with other study populations. [7] One advantage of this large cohort of 582 pwMS is that extensive clinical summaries are available for each donor, to allow accurate categorisation of disease milestones, trajectories, and cause of death. In addition, it was possible to include cases regardless of whether MS was mentioned on the death certificate, in contrast to previous studies on mortality in MS.[9, 10] Indeed, in our cohort, MS was not mentioned on the death certificate in 35.9% of cases, many of which we adjudged to have died an MS-related death after inspection of clinical records. Furthermore, by manually categorising UCD in each patient, we mitigated the effect of heterogeneous death

certification technique and coding rule changes which can lead to inconsistent reporting of UCD within other studies.[10-12]

The most important limitation of this study was that data were retrospectively collated from clinical records and notes. The required data was not apparent on occasion, for example the ‘date of wheelchair use’ may not have been documented, while on other occasions coding of data required interpretation by the assessor. However, care was taken to formulate standardised rules for coding, and the availability of clinical notes improved reliability of data over death certificates. Overall, manual determination of these factors was considered to be a strength of this study as it allowed a more thorough analysis of each case, using the clinical summary where necessary. Another possible limitation is that cases were included whose deaths occurred between 1998 and 2015. Standards of care may have changed over this period, although the results reported in this study appeared consistent over time.

The most common cause of death was pneumonia (46%), followed by MS (14.8%), and cancer (10.1%). The rates of pneumonia and MS deaths are different to those found in other studies,[12, 13] however this is due to methodological differences; UCD was only classed as MS where no other cause was available, in order to allow more specific analysis of cause of death. Diseases of the respiratory system accounted for 15% of deaths in the UK in 2013 and therefore are far more common in our MS cohort.[14] Cancer is the most common cause of death among the general population (29%) followed by diseases of the circulatory system (28%); both much higher rates than in our cohort.[14] Accidents and suicide accounted for 1.2% of deaths in our sample, equal to rates in the UK general population in 2013.[14, 15] Although only 14.8% of death certificates directly attributed UCD to MS, 72.5% of deaths were MS-related. Younger age at symptom onset, wheelchair use,

progression and death, as well as a shorter disease course, were all associated with MS-related death. This earlier achievement of disease milestones and shorter interval between milestones is suggestive of a more aggressive disease course; those who evade this aggressive disease course are more prone to the same causes of death as the general population.

This study found that 73.7% of pwMS had a progressively dwindling trajectory prior to death. This is in contrast to the general ageing population, in which 40% of the population progressively dwindle.[2] Those who progressively dwindled experienced an earlier age at symptom onset, progression, wheelchair use, and death than those experiencing other trajectories, indicating that earlier disease milestones predict progressive dwindling.

In 2006, 58% of general population deaths in the UK were in hospital and only 35% of people died at home or in a care home, despite 56-74% of people saying they would prefer to die at home.[16, 17] As a result of this majority preference for dying at home, place of death is often considered a surrogate marker of the success of end of life care. Of 503 pwMS in this study, 50.8% died in hospital, 25.4% died in a care home, 18.9% died in their own residence, and 4.5% died in a hospice, consistent with previous work.[10] Those who died following a progressive dwindling trajectory were as likely to die in hospital as any other group, a statistic that might be improved with the implementation of formative care pathways for this group, as the nature of the trajectory allows time to discuss patient preferences and establish appropriate plans. Major barriers to dying in the community include poor provision of end of life care services by general practices, insufficient community nursing staff, poor coordination of services, and lack of access to home modifications and out-of-hours medicines.[18] MS patients may be more vulnerable to these service deficiencies, as

a result of their comparably young age, complex care needs and increased rates of cognitive disability.[19] Implementation of a structured package of formative care, with discussions at various stages of the process, would give pwMS opportunities from an early stage, to communicate how they wish to live, and die, as well as providing a more suitable and coordinated care network to meet their requirements.

As people approach death, an increasing number of pwMS and their caregivers desire support from palliative care services either at home or in hospices.[17, 20, 21] In our study, those who died an MS-related death were far less likely to die in a hospice than those who died a non-MS related death, suggesting hospice services seldom offer palliative care to those dying of MS, despite previous research showing similarities between MS and cancer in the prevalence of palliative-care-related problems, and the need for more palliative care services for pwMS.[22, 23] Even in the general population, it is estimated that 69%-82% of those who die need palliative care, whereas in our study only 4.6% of pwMS died in a hospice, most of whom also had cancer.[24] Randomised controlled trials in pwMS have shown that palliative care can improve patient-reported outcomes, care-giver burden, and are cost-effective.[25-27] Difficulties in determining prognosis can lead to lack of utilisation of end of life care services by those with non-malignant diseases as healthcare professionals may be unsure when to begin the transfer to these services.[28, 29] The use of predictors of progressive dwindling, with a transfer to formative care pathways may improve quality of life for these patients in the progressive stage of their disease, and because of the overlap in techniques, may increase scope for smooth transition into palliative care in the home or hospice environment.[29] An ongoing randomised controlled trial from Solari et al is examining the strengths and limitations of a home-based end-of-life care approach in people with severe MS; this

should provide insight into the impact of, for example, home pain management services on MS symptoms and health-related quality of life, an important aspect of formative care.[30]

A qualitative study by Borreani et al. of pwMS, their carers and health professionals, found that adapting to life with disability was of greater importance than end of life care.[31] The interventions proposed in response to their findings implied a formative approach, including domestic support, rehabilitation and psychosocial intervention.[31]

Future work should develop ways to improve the delivery of formative care, assess its acceptability, and whether it could be delivered in complex situations. Input from pwMS and their families is paramount in developing such pathways. Further work could build a quantitative tool to allow clinicians to assess the exact risk of progressive dwindling for an individual patient with a specific combination of risk factors. Such a tool might be utilised to deliver formative care approaches to targeted patient populations, and to evaluate their impact on symptom relief, quality of life, place of death, cost of healthcare, and benefit to carers and family members.

Conclusion

End of life care has been failing a large number of patients because of uncoordinated services, lack of communication and lack of identification of people who are dying.[3] Formative care, when not properly designated as such can be disjointed and inadequate from the patient and family's perspective and unnecessarily expensive from a service provider's angle.[1] This study concludes

that these failings might impact particularly upon pwMS, as 73.7% of pwMS followed the progressively dwindling trajectory to death. A marker of these failings lies in the finding that pwMS who progressively dwindle are no less likely to die in hospital than those with other trajectories to death. Ideally, those who progressively dwindle should have lower rates of hospital deaths, as a result of well-timed discussions, adequate planning and well-coordinated formative and palliative care services. This study aimed to identify factors associated with progressive dwindling and found that early disease milestones such as age at onset, progression and wheelchair use can be used as potential predictors, thus allowing timely discussions, a vital step towards providing formative care to those who need it. This study found that 72.5% of pwMS died an MS-related death, and this too was associated with an aggressive early disease course. The use of predictors of progressive dwindling, with a transfer to formative care pathways for years prior to death may improve quality of life for patients in the progressive stage of their disease and their caregivers, and may increase scope for smooth transition into palliative care in the home or hospice environment. We believe that better coordination of medical and social care is paramount in the years prior to death but subsequent to active treatment in pwMS and other populations. The results from this study provide a framework on which to base subsequent carestrategies, and to target those who might benefit most from formative care.

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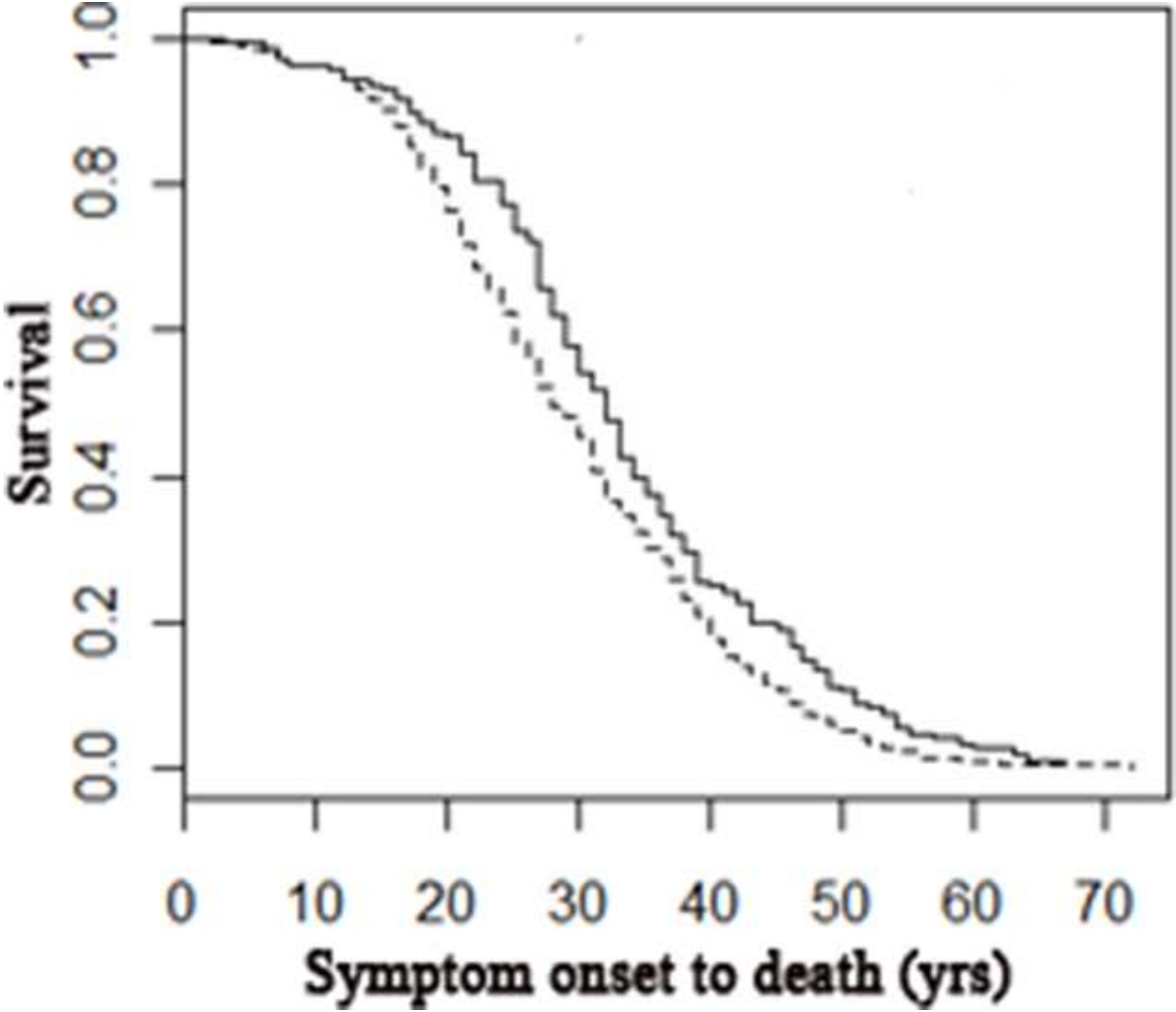
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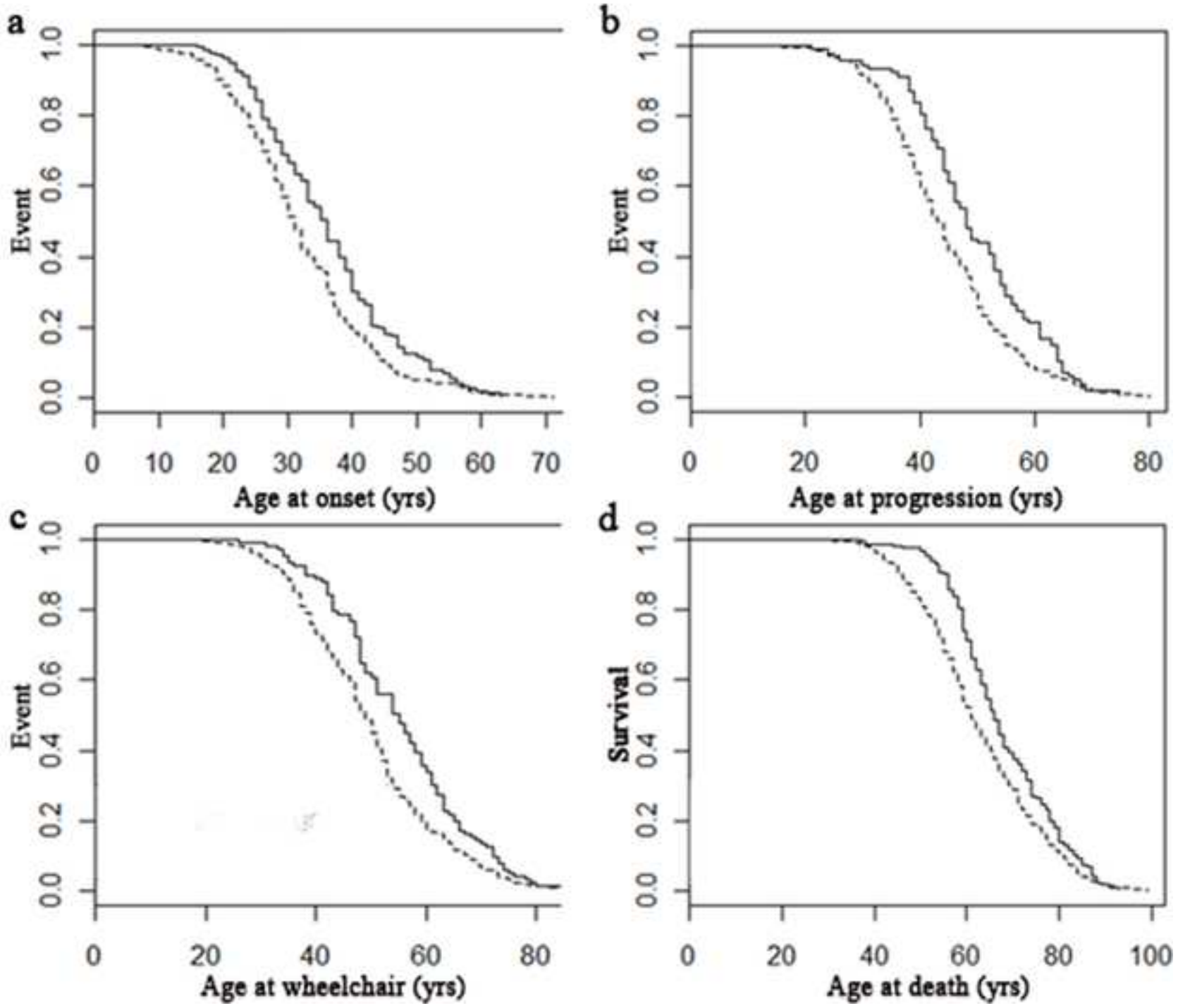
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Progressive Dwindling in Multiple Sclerosis: An Opportunity to Improve Care

Short title: Progressive Dwindling in Multiple Sclerosis

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Key words: Multiple sclerosis, formative care, trajectory to death

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Abstract

Introduction: In the general ageing population, 40% of deaths occur following a prolonged trajectory of 'progressive dwindling', characterised by chronic accumulation of disability and frailty, and associated with increased dependency and reduced reserves. Those who progressively dwindle are poorly catered for by current healthcare systems and would benefit from a coordinated approach to their medical and social care, known as formative care. People with multiple sclerosis (pwMS) may be more likely to progressively dwindle, and may be appropriate targets for formative care pathways.

Objectives: To determine the proportion of pwMS who follow a progressive dwindling trajectory prior to death. To relate trajectory to place of death, and examine what factors predict the progressively dwindling trajectory.

Methods: A retrospective observational study of 582 deceased pwMS enrolled in the UK MS Tissue Bank, including death certificates and extensive clinical summaries.

Results: 73.7% of pwMS had a 'progressively dwindling' trajectory of dying. This was predicted by those who reach MS disease milestones earlier. 72.5% of pwMS died an MS-related death, which was predicted by an aggressive disease course from onset. Those who progressively dwindled were equally likely to die in hospital as those with other trajectories to death.

Conclusions: The progressively dwindling trajectory of dying is very common in pwMS, and can be predicted by earlier disease milestones. Pathways could target pwMS in these years prior to death, to improve care.

Introduction

Over the last century there has been a shift in the commonest causes of death, from acute causes at a young age, to a substantially lengthened lifespan characterised by a period of progressive chronic illness before death.[1] Bowman and Meyer (2014) described four broad trajectories of dying in an ageing population:[2]

- 20% are sudden e.g. myocardial infarction;
- 20% of deaths follow a short period of rapid decline after a 'clear clinical transition' from treatable to progressive e.g. cancer;
- 20% occur as a result of acute exacerbations of a progressive long-term disease e.g. chronic obstructive pulmonary disease;
- 40% of deaths occur following a prolonged period of 'progressive dwindling' e.g. Alzheimer's disease.

For the first three trajectories, healthcare infrastructure is well established and effective, with preventative and emergency medicine for the sudden trajectory, palliative care for those with a short period of rapid decline, and specialist chronic disease management programmes for those with progressive long-term diseases with acute exacerbations.[2] However, there is a lack of appropriate pathways for those who 'progressively dwindle', with often haphazard involvement of a wide range of healthcare professionals and services, and thus care can be sub-optimal.[2] A report from the UK Parliamentary and Health Service Ombudsman in May 2015 found a lack of coordination of care services, delays in referral and inadequate out-of-hours services have led to poor end of life care for a large number of patients.[3] The report suggested this could be improved by proper service delivery and organisation.[3] The term 'formative care' has been coined to describe the strategy of "enabling the best possible life quality and experience in the context of a life

reframed by frailty and dependency" for progressively dwindling patients in the time between active treatment and end of life care.[2] Aspects of formative care overlap with palliative care, including symptom relief and home care, although formative care focuses on maximising quality of life rather than quality of death, and takes place over years rather than weeks or months. Elements of formative care might include access to regular tailored physiotherapy, occupational therapy visits to the home environment, nutritional support, pathways to determine when packages of care should be escalated and improving this transition, and rationalising medication, focusing on those that improve quality of life. Promoting implementation of formative care from an early stage will also allow improved transition into palliative care, and act as a buffer against difficulties in determining when palliative care should begin. Identifying markers to predict those who will adopt a progressive dwindling trajectory will be essential for implementing formative care in a timely manner for these patients.

People with MS (pwMS) have a prolonged disease course, often 50 years or more.[4] Disease modifying therapies are available for relapsing MS, but there are currently no licensed treatments for the progressive phase. As a result, a gap in structured care pathways has arisen between active treatment and end of life care, in which pwMS may spend a prolonged period 'progressively dwindling', with considerable distress associated with decline in physical and mental function.[5] This period without active treatment but before palliation is not specific to MS, but is particularly pertinent due to the extended and unpredictable timeframe. It is during this phase that pwMS could greatly benefit from formative care. Those pwMS who progressively dwindle experience a slow and steady accumulation of disability,

resulting in frailty, and associated with increased dependency and reduced physiologic reserve.[6] This period extends for many years before death, during which time there is an increasing burden of care, often taken on by the family, and punctuated by superimposed illness. As the ever-reducing physiologic reserve resets the baseline, there is reduced capacity to cope with said periods of superimposed illness, such as pneumonia, and ultimately these present the terminal event.[6] Because formative care promotes adequate planning of and improved transition to palliative care due to overlap in techniques, it should also empower patients to choose to die at home, if this is their wish. To understand how formative care might help pwMS, this study aimed to: (i) determine the frequency of progressive dwindling in an MS population, (ii) identify factors associated with~~predictors of~~ progressive dwindling, (iii) determine specific cause of death and whether deaths were ultimately MS-related or not, and (iv) examine place of death in those with different trajectories to death.~~and to characterise place of death in those with different trajectories to death. This study also examines whether deaths were MS-related or not, and specific cause of death. This study finds rates of progressive dwindling in pwMS far greater than in the general population. Progressive dwindling can be predicted in pwMS by early markers of aggressive disease, and is not associated with a different place of death.~~

Materials and Methods

Data collection

Data were retrospectively collated from a cohort of ~~597~~582 pwMS who had died between January 1998 and February 2015 inclusive, and had been registered on the UK MS Tissue Bank (UKMSTB)~~,~~. The UKMSTB is a national scheme to collect post-mortem tissue donated from pwMS and non-MS controls, as well as death certificate data, clinical summaries and extensive clinical notes. ~~a large observational community based population of pwMS and controls.~~ As of February 2015, the UKMSTB stored post-mortem data on 606 pwMS; all were included in this study after exclusion of 9 donors without a confirmed tissue diagnosis of MS, and ~~–~~15 ~~participants were excluded from the study as there was~~ donors with insufficient data on cause of death. Clinical notes were used to define the date of symptom onset, progressive disease (defined as a period of at least one year with gradual disability worsening without relapses), wheelchair use, and death, for all patients. Participants with missing data on symptom onset, progression, wheelchair use, and/or place of death were included in the study, but were excluded from relevant analyses. The UKMSTB has ethical approval from the London Multicenter Research Ethics Committee (MREC/02/2/39) to prospectively recruit donors after obtaining written informed consent, and accrue an extensive clinical summary from medical notes and death certificates as previously described.[7] ~~Raw data has not been provided as it contains patient identifiable information, and is custody of the UK MS Tissue Bank. Requests for data can be made to the UK MS Tissue Bank via Dr Richard Nicholas (r.nicholas@imperial.ac.uk).~~

Classification of death: Cause, MS-related, Trajectory, and Place

Death certificate entries were used to categorise underlying cause of death (UCD), and confirmed using patient notes and clinical summaries when the death certificate was unclear. For example, if the death certificate stated 'infection' or 'respiratory failure', clinical notes were used to identify a more specific UCD e.g. pneumonia. If multiple causes were listed on the death certificate, clinical notes were used to discern the primary cause of death. ~~UCD was only categorised as MS when no other cause was listed; where possible a more specific cause (e.g. pneumonia) was used, even if secondary to MS.~~ If multiple causes of death were listed, the diagnosis that triggered the chain of events leading to death was chosen (e.g. pneumonia leading to respiratory failure). Where it could not be discerned whether one was more responsible that the other (e.g. pneumonia and UTI), and the clinical notes did not clarify, the first listed was used as the UCD. UCD was only categorised as MS when no other cause was listed; where possible a more specific cause (e.g. pneumonia) was used, even if secondary to MS. ~~-~~Deaths were also classified as being 'related to MS' or not, by examining death certificates and clinical notes. Trajectory to death categories were adapted from Bowman and Meyer;[2] trajectory was based on cause of death and review of the clinical summaries. Place of death categories were based on Public Health England's place of death classification.[8] Own residence, care home and hospice deaths were also combined into a 'community' category.

Statistical analysis

~~Analyses included Student's t-test, chi-squared test, one-way between subjects ANOVA, and Cox proportional hazards regression.~~ Cox proportional hazards regression was performed to compare survival from disease milestones between

different groups e.g. those with MS-related deaths vs. those with non-MS-related deaths, those who progressively dwindled vs. those with other disease trajectories. Disease milestones were compared between all four disease trajectory groups using one way between subject ANOVA, with Tukey HSD used post hoc for significant ANOVA analyses. Student's t-test was used to compare demographics in males and females. Parametric tests were performed after testing for normality. Chi-squared test was used to compare location of death in those with different trajectories to death, and those with and without MS-related deaths. Yates' chi-squared test was used to avoid overestimation of statistical significance. Where chi-squared revealed significance in contingency tables greater than 2x2, further post hoc 2x2 chi-squared tests were carried out to identify the significant values, with criteria for statistical significance adjusted according to the number of post hoc tests carried out. ~~Tukey HSD was used post hoc for significant ANOVA analyses.~~

Results

Study population and cause of death

582 deceased pwMS were included in the analysis. 70% were female, and the average age at symptom onset was later among females than males (34.1±10.7 [mean±SD] vs 30.6±9.7 p<0.001). The average age of progression was 45.5±11.3, the average age of wheelchair use was 50.6±12.8 and the average age at death was 63.8±12.7 years with women dying later than men (64.9±13.1 vs 61.2±11.5, p<0.01). 68.5% were categorised as secondary progressive MS at the time of death, 11.4% primary progressive, 6.0% relapsing remitting, and the sub-type of MS was unavailable in 14.1%. The most common UCD was pneumonia or bronchopneumonia (37.5%), followed by MS (14.8%), cancer (10.1%), and aspiration pneumonia (8.6%; Table 1). 72.5% died an MS-related death. 35.9% of pwMS did not have MS recorded on any part of their death certificate; including 28.7% of those whose death was adjudged to be MS-related after inspection of clinical notes in this study.

Table 1. **Cause of death of 582 people with MS, UKMSTB January 1998 to February 2015.**

Cause of death specific categories	n (%)
Multiple sclerosis	86 (14.8)
Pneumonia, bronchopneumonia	218 (37.5)
Aspiration pneumonia	50 (8.6)
Urinary tract infection	34 (5.8)

Other infection, inc. sepsis	12 (2.1)
Acute cardiovascular event	22 (3.8)
Acute cerebrovascular event	18 (3.1)
Pulmonary embolism	14 (2.4)
Non-acute cardiac e.g. senile myocardium or heart failure	11 (1.9)
Respiratory failure	9 (1.5)
Infection secondary to chronic obstructive pulmonary disease	7 (1.2)
Cancer	59 (10.1)
Acute abdomen e.g. obstruction	13 (2.2)
Suicide	7 (1.2)
Epilepsy	3 (0.5)
Other e.g. fulminant liver failure, renal failure, dehydration, acute pyelonephritis, tuberculosis, old age, myelodysplastic syndrome, liver abscess, progressive multifocal leukoencephalopathy, general deterioration, anaphylactic reaction, cardiac asthenia amyloid, ruptured left subclavian artery aneurysm, necrotic fasciitis, accidents, dementia, and frailty.	19 (3.1)

MS-related deaths are predicted by markers of aggressive disease

Of the 582 pwMS, 72.5% died an MS-related death. MS-related deaths were associated with younger age at symptom onset (MS-related: 31.6±9.9; non MS-

related 36.9±10.9, p<0.0001), progression (MS-related: 43.5±10.3; non MS-related 51.3±11.9, p<0.0001), wheelchair use (MS-related: 48.4±11.9; non MS-related 57.6±12.9, p<0.0001) and death (MS-related: 61.5±12.4; non MS-related 68.9±11.6, p<0.0001). MS-related deaths were also associated with a shorter time from symptom onset to death (MS-related: 29.4 ±11.9; non MS-related 32.9±12.7, p<0.01). These earlier milestones are indicative of more aggressive disease courses leading to MS-related deaths (Figure 1).

Figure 1. Cox proportional hazard regression model comparing disease length leading to MS-related deaths and unrelated deaths.

Those whose death was MS-related had a shorter disease course from symptom onset to death than those whose death was unrelated (R^2=0.016, n=504, p<0.01; MS death 1.32, 95CI 1.08-1.61). Dotted line represents MS-related deaths; solid line represents non-MS-related deaths.

Progressive dwindling is a common trajectory in MS, and is predicted by earlier disease milestones

Of 582 pwMS, 429 (73.7%) progressively dwindled, 76 died a sudden death, 59 experienced a clear clinical transition from a treatable to an unrelenting progressive disease (e.g. cancer), and 18 died as a result of an acute exacerbation of a progressive long-term condition. When comparing those who progressively dwindled with the other trajectories combined, those who progressively dwindled had earlier age at onset, progression, wheelchair use and death (all p<0.01; Figure 2). Differences between groups remained when comparing individual groups in a one-

way between subjects ANOVA (Table 2). More specifically, after post-hoc Tukey HSD, those who progressively dwindled had a mean age at MS onset five years earlier than those who died suddenly ($p<0.01$). Those who experienced a progressive dwindling trajectory had an earlier age at progression than those who died following a clear clinical transition ($p<0.05$) or an acute exacerbation ($p<0.01$). Those who experienced a progressive dwindling course were wheelchair-bound 9 years earlier than those who died following acute exacerbations and 5 years earlier than those who died suddenly (both $p<0.05$). Those who progressively dwindled died at a younger age than those who experienced any other trajectory to death (all $p<0.05$). There was no significant relationship between the trajectory to death and interval from symptom onset to death.

Figure 2. Cox proportional hazard regression models of disease milestones in those who progressively dwindle compared to other trajectories.

Those who progressively dwindle had an earlier age at onset (A, $R^2=0.02$, n=504, $p<0.01$; Progressive dwindling: 1.08, 95CI 1.03-1.14), progression (B, $R^2=0.024$, n=390, $p<0.01$; Progressive dwindling :1.09, 95CI 1.03-1.16), wheelchair use (C, $R^2=0.022$, n=462, $p<0.01$; Progressive dwindling: 1.09, 95CI 1.03-1.15) and death (D, $R^2=0.014$, n=582, $p<0.01$; Progressive dwindling: 1.07, 95CI 1.02-1.12). Dotted lines represent those with progressive dwindling trajectory to death; solid line represents all other disease trajectories.

Table 2. Different Trajectories association with MS milestones.

Trajectories	Mean age at symptom onset ±SD (n)	Mean age at progression ±SD (n)	Mean age at wheelchair ±SD (n)	Mean age at death ±SD (n)
Clear clinical transition	35.3±10.0 (54)	50.2 ±9.9 (38)	54.2±10.6 (39)	67.7±10.2 (59)
Acute exacerbation of progressive long-term condition	35.5±10.4 (15)	54.5±15.3 (12)	58.5±13.6 (13)	71.2±9.2 (18)
Sudden	36.9±10.7 (65)	47.1±10.4 (42)	54.4±13.0 (56)	66.5±12.1 (76)
Progressive dwindling	32.0±10.3 (370)	44.3±11.1 (298)	49.3±12.6 (354)	62.5±13.0 (429)
ANOVA Significance	p<0.01	p<0.001	p<0.001	p<0.001

The significant associations as identified by post-hoc Tukey HSD are detailed under ‘Progressive dwindling is a common trajectory in MS, and is predicted by earlier disease milestones’.

Location of death~~Those who progressively dwindle are equally likely to die in hospital~~

Of ~~503 pwMS in whom~~ 582 donors included in the study, place of death was available for 503 donors (86.4%). Of those, 50.7% died in hospital, 25.4% died in a care home, 18.9% died in their own residence, 4.6% died in a hospice and 2 died in other locations. Those who progressively dwindled were equally likely to die in hospital as those with other trajectories to death (Table 3).

Table 3. Community vs. hospital and trajectory to death

	Community n (%)	Hospital n (%)	Total
1 Clear clinical transition ~~from treatable to unrelenting progression~~	33 (61.1)	21 (38.9)	54
2 Acute exacerbations of progressive long-term conditions	3 (23.1)	10 (76.9)	13
3 Sudden	32 (47.8)	35 (52.2)	67
4 Progressive dwindling	178 (48.5)	189 (51.5)	367
Total	246 (49.1)	255 (50.9)	501

NB: two died in 'other' locations which were not classified into community or hospital.
Own residence, care home and hospice deaths were combined into a 'community' category.

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Similarly, those whose death was MS-related were equally likely to die in hospital as those whose death was unrelated to MS (Table 4). Those with MS-related deaths were less likely to die in a hospice – a category dominated by those with cancer-related deaths. Dying in the community rather than in hospital was not associated with an earlier death or a shorter interval from symptom onset to death.

Table 4. The relationship between place of death and whether a death was MS-related.

Significantly lower numbers of subjects died an MS-related death in hospices compared to those who had a non MS-related death ($p<0.01$, χ^2 test).

	MS-related death n (%)	**Not MS-related death n (%)**
1 Own residence	67 (70.5)	28 (29.5)
2 Hospital	184 (72.2)	71 (27.8)
3 Care homes	98 (76.6)	30 (23.4)
4 Hospice	9 (39.1)	14 (60.9)
5 Other†	0	2
Total	358 (71.2)	145 (28.8)

† excluded from χ^2 test

Discussion

This study finds rates of progressive dwindling in pwMS far greater than in the general population. These results emphasise the extended and unpredictable timeframe between active treatment and end of life care in MS, and the high proportion of pwMS who have prolonged periods of frailty, dependency, and reduced physiological reserve for many years prior to death. Those who progressively dwindle are equally likely to die in hospital as those with more acute trajectories to death, which might be interpreted as a failure of care. This study also finds that progressive dwindling can be predicted by early markers of aggressive disease in pwMS, suggesting an opportunity for targeted formative care in this subset of patients.

~~This is the first study to look at the frequency of trajectory to death in the MS population, and factors which predict it. We find that progressive dwindling is far more common in MS than in the general population, and is predicted by reaching disease milestones earlier. Those who progressively dwindle are equally likely to die in hospital as those with more acute trajectories to death.~~ The UKMSTB is a community based scheme where people with MS register during their lifetime for tissue and clinical data to be collected when they die. ~~The milestones and MS sub-types of donors in the UKMSTB are similar to other cohorts.~~Donors are representative of MS patients nationwide as a result of a national community-based recruitment strategy, with accurate representation of clinical milestones and MS sub-types confirmed by comparison with other study populations. [7] One advantage of this large cohort of 582 pwMS is that extensive clinical summaries are available for

each donor, to allow accurate categorisation of disease milestones, trajectories, and cause of death. In addition, it was possible to include cases ~~are included~~ regardless of whether MS was mentioned on the death certificate, in contrast to previous studies on mortality in MS.[9, 10] Indeed, in our cohort, MS was not mentioned on the death certificate in 35.9% of cases, many of which we adjudged to have died an MS-related death after inspection of clinical records. Furthermore, by manually categorising UCD in each patient, we mitigated the effect of heterogeneous death certification technique and coding rule changes which can lead to inconsistent reporting of UCD within other studies.[10-12]

The most important limitation of this study was that data were retrospectively collated from clinical records and notes. The required data was not apparent on occasion, for example the 'date of wheelchair use' may not have been documented, while on other occasions coding of data required interpretation by the assessor. However, care was taken to formulate standardised rules for coding, and the availability of clinical notes improved reliability of data over death certificates. Overall, manual determination of these factors was considered to be a strength of this study as it allowed a more thorough analysis of each case, using the clinical summary where necessary. Another possible limitation is that cases were included whose deaths occurred between 1998 and 2015. Standards of care may have changed over this period, although the results reported in this study appeared consistent over time.

The most common cause of death was pneumonia (46%), followed by MS (14.8%), and cancer (10.1%). The rates of pneumonia and MS deaths are different to those found in other studies,[12, 13] however this is due to methodological differences; UCD was only classed as MS where no other cause was available, in order to allow more specific analysis of cause of death. Diseases of the respiratory system

accounted for 15% of deaths in the UK in 2013 and therefore are far more common in our MS cohort.[14] Cancer is the most common cause of death among the general population (29%) followed by diseases of the circulatory system (28%); both much higher rates than in our cohort.[14] Accidents and suicide accounted for 1.2% of deaths in our sample, equal to rates in the UK general population in 2013.[14, 15] Although only 14.8% of death certificates directly attributed UCD to MS, 72.5% of deaths were MS-related. Younger age at symptom onset, wheelchair use, progression and death, as well as a shorter disease course, were all associated with MS-related death. This earlier achievement of disease milestones and shorter interval between milestones is suggestive of a more aggressive disease course; those who evade this aggressive disease course are more prone to the same causes of death as the general population.

This study found that 73.7% of pwMS had a progressively dwindling trajectory prior to death. This is in contrast to the general ageing population, in which 40% of the population progressively dwindle.[2] Those who progressively dwindled experienced an earlier age at symptom onset, progression, wheelchair use, and death than those experiencing other trajectories, indicating that earlier disease milestones predict progressive dwindling.

In 2006, 58% of general population deaths in the UK were in hospital and only 35% of people died at home or in a care home, despite 56-74% of people saying they would prefer to die at home.[16, 17] As a result of this majority preference for dying at home, place of death is often considered a surrogate marker of the success of end of life care. Of 503 pwMS in this study, 50.8% died in hospital, 25.4% died in a care home, 18.9% died in their own residence, and 4.5% died in a hospice, consistent with previous work.[10] Those who died following a progressive dwindling trajectory

were as likely to die in hospital as any other group, a statistic that might be improved with the implementation of formative care pathways for this group, as the nature of the trajectory allows time to discuss patient preferences and establish appropriate plans. Major barriers to dying in the community include poor provision of end of life care services by general practices, insufficient community nursing staff, poor coordination of services, and lack of access to home modifications and out-of-hours medicines.[18] MS patients may be more vulnerable to these service deficiencies, as a result of their comparably young age, complex care needs and increased rates of cognitive disability.[19] Implementation of a structured package of formative care, with discussions at various stages of the process, would give pwMS opportunities from an early stage, to communicate how they wish to live, and die, as well as providing a more suitable and coordinated care network to meet their requirements.

As people approach death, an increasing number of pwMS and their caregivers desire support from palliative care services either at home or in hospices.[17, 20, 21] In our study, those who died an MS-related death were far less likely to die in a hospice than those who died a non-MS related death, suggesting hospice services seldom offer palliative care to those dying of MS, despite previous research showing similarities between MS and cancer in the prevalence of palliative-care-related problems, and the need for more palliative care services for pwMS.[22, 23] Even in the general population, it is estimated that 69%-82% of those who die need palliative care, whereas in our study only 4.6% of pwMS died in a hospice, most of whom also had cancer.[24] Randomised controlled trials in pwMS have shown that palliative care can improve patient-reported outcomes, care-giver burden, and are cost-effective.[25-27] Difficulties in determining prognosis can lead to lack of utilisation of end of life care services by those with non-malignant diseases as healthcare

professionals may be unsure when to begin the transfer to these services.[28, 29] The use of predictors of progressive dwindling, with a transfer to formative care pathways may improve quality of life for these patients in the progressive stage of their disease, and because of the overlap in techniques, may increase scope for smooth transition into palliative care in the home or hospice environment.[29] An ongoing randomised controlled trial from Solari et al is examining the strengths and limitations of a home-based end-of-life care approach in people with severe MS; this should provide insight into the impact of, for example, home pain management services on MS symptoms and health-related quality of life, an important aspect of formative care.[30]

A qualitative study by Borreani et al. of pwMS, their carers and health professionals, found that adapting to life with disability was of greater importance than end of life care.[31] The interventions proposed in response to their findings implied a formative approach, including domestic support, rehabilitation and psychosocial intervention.[31] ~~An ongoing randomised controlled trial from Solari et al. will examine the strengths and limitations of a home-based end-of-life care approach in people with severe MS; this should provide insight into the impact of, for example, home pain management services on MS symptoms and health-related quality of life, an important aspect of formative care.~~

Future work should develop ways to improve the delivery of formative care, assess its acceptability, and whether it could be delivered in complex situations. Input from pwMS and their families is paramount in developing such pathways. Further work could build a quantitative tool to allow clinicians to assess the exact risk of

progressive dwindling for an individual patient with a specific combination of risk factors. Such a tool might be utilised to deliver formative care approaches to targeted patient populations, and to evaluate their impact on symptom relief, quality of life, place of death, cost of healthcare, and benefit to carers and family members.

Conclusion

~~In the general population, the majority of people experience several years of disability and frailty before death and 40% progressively dwindle.[2] The burden of chronic illness and disability at the end of life, intertwined with that of an ageing population, is exponentially increasing.[1] Causes of death and the utilisation of services reflect this, with over 20% of healthcare spending occurring during the last year of life.[32]~~ End of life care has been failing a large number of patients because of uncoordinated services, lack of communication and lack of identification of people who are dying.[3] Formative care, when not properly designated as such can be disjointed and inadequate from the patient and family's perspective and unnecessarily expensive from a service provider's angle.[1] This study concludes that these failings might impact particularly upon pwMS, as 73.7% of pwMS followed the progressively dwindling trajectory to death. ~~We have shown that progressive dwindling is even more common in MS, especially in those patients reaching disease milestones earlier.~~ A marker of these failings lies in the finding that pwMS who progressively dwindle are no less likely to die in hospital than those with other trajectories to death. Ideally, those who progressively dwindle should have lower rates of hospital deaths, as a result of well-timed discussions, adequate planning and well-coordinated formative and palliative care services. This study aimed to identify

factors associated with progressive dwindling and found that early disease milestones such as age at onset, progression and wheelchair use can be used as potential predictors, ~~These results highlight the fact that disease milestones can be used to predict progressive dwindling in specific patient groups,~~ thus allowing timely discussions, a vital step towards providing formative care to those who need it. This study found that 72.5% of pwMS died an MS-related death, and this too was associated with an aggressive early disease course. The use of predictors of progressive dwindling, with a transfer to formative care pathways for years prior to death may improve quality of life for patients in the progressive stage of their disease and their caregivers, and may increase scope for smooth transition into palliative care in the home or hospice environment. We believe that better coordination of medical and social care is paramount in the years prior to death but subsequent to active treatment in pwMS and other populations. The results from this study provide a framework on which to base subsequent care~~treatment~~ strategies, and to target those who might benefit most from formative care.

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Dear Editor and Reviewers,

We are very grateful for the reviewers' comments regarding the manuscript "Progressive Dwindling in Multiple Sclerosis: An Opportunity to Improve Care". We believe that all reviewer comments have now been addressed, and the manuscript is much improved as a result. Please find attached a revised manuscript with 'tracked changes', and a clean version of the revised manuscript. In addition, we have addressed each reviewer comment (written in red) in turn, below.

Reviewer: 1

Comments to the Author: This is a really interesting paper that attempts to examine progressive dwindling among those living with and dying from MS and to examine place of death for this patient group. Thank you for letting me review it.

I see a number of important messages here but they need to be dissected to better effect. Often the message about how we can care for this group of patient and fulfil their wishes at the end of life is forgotten or omitted. This need to be teased out more from the introduction all the way through the conclusion which is rather bland and tells us little we did not know already. Nothing on research direction is future either. What more do we still need to know that is not answer by this study. I have made the following suggestions to improve this already interesting and important paper.

We are very grateful to Reviewer 1 for taking the time to make constructive criticism on how this manuscript could be improved. We agree with all comments, and think that the manuscript has benefitted greatly from changes made in response to Reviewer 1's comments. There is now more emphasis on what exactly formative care is, what progressive dwindling is, and how people with MS could benefit from formative care. It is more clearly described how this manuscript contributes to what is already known. Future research is now addressed. More detailed responses to each comment are given below.

1. *Clear abstract in places, but more about albeit briefly what exactly progressive dwindling actually is.*

The opening sentence of the abstract has been improved to the following: "In the general ageing population, 40% of deaths occur following a prolonged trajectory of 'progressive dwindling', characterised by chronic accumulation of disability and frailty, and associated with increased dependency and reduced reserves". We agree that this makes the abstract more accessible to the general audience.

2. *Why place of death? Why is this a critical variable to examine? This may seem intuitive and common sense to some but it need to be highlighted that location of death is regarded by some as a marker of success in care in relation to achieving preferences at the end of life.*

Thank you for this comment. We agree that location of death is regarded as a marker of success in end-of-life care – this has now been stated in the discussion. Additional references have been added, including Gomes et al 2012, and others specific to MS. The role of palliative care in MS (either at home or in hospices) has also been discussed more widely.

3. *Conclusions section does not match objectives of study. In what ways can/should care improve, and why?*

   Large parts of the conclusion have been rewritten, to more closely address the objectives of the study. Failings in care are highlighted, and suggestions made for future research and opportunities to improve care. We hope that the reviewer thinks the new conclusion is an improvement.

4. *Useful introduction. But please tell the reader how you or others define progressive dwindling (more than on page 5 for example). Scott Murray's paper in the BMJ helpfully explain that this patient group.. This progressive disability relates to those who are …from an already low baseline of cognitive or physical functioning. Such patients may lose weight and functional capacity and then succumb to minor physical events or daily social "hassles" that may in themselves seem trivial but, occurring in combination with declining reserves, can prove fatal Illness trajectories and palliative care (BMJ 330 2005) I understand this group to be as follows: They are likely to lose their ability to take care of themselves long before death. As a result, they ordinarily require intensive personal care throughout their period of dependency. This imposes substantial burdens on both paid and volunteer (usually family) caregivers. These patients usually experience a slow worsening of self-care, with occasional episodes of more serious infections or other illnesses. Some patients may get a substantial illness that takes their life abruptly, especially when all concerned have decided not to pursue aggressive treatment to prolong life.*

   We agree that progressive dwindling was not adequately defined, especially for the general reader. We have now added the following: "Those who progressively dwindle experience a slow and steady accumulation of disability, resulting in frailty, and associated with increased dependency and reduced physiologic reserve. This period extends for many years before death, during which time there is an increasing burden of care, often taken on by the family, and punctuated by superimposed illness. As the ever-reducing physiologic reserve resets the baseline, there is reduced capacity to cope with said periods of superimposed illness, such as pneumonia, and ultimately these present the terminal event." Thank you for the comment.

5. *More on location of death. We now know from multiple studies for example what preferences are but this needs to be beefed up a bit. Refer to among others. Gomes et al Preferences for place of death if faced with advanced cancer: a population survey in England, Flanders, Germany, Italy, the Netherlands, Portugal and Spain Ann Oncol. 2012 Aug;23(8):2006-15. Epub 2012 Feb 16.*

   As above, more has now been written about location of death, dying at home, and the need for palliative care services in MS. Gomes et al have been cited, as have other studies.

6. *Think carefully how aims (an study objectives are laid out as they are quite diffuse at the moment. Better as follow I think … This study aimed to (i) to examine frequency of progressive dwindling among an MS population; (ii) to identify factors associated with of progressive dwindling; (iii) to examine the specific cause of death among this patient group (iv) to identify place of death in those with different trajectories to death.*

Thank you. We agree that this paragraph is an improvement on our original, and states the study aims more clearly. We have copied the style of the reviewer's paragraph (with only minor changes) – we hope that is ok.

7. *This need to be moved somewhere else …it is not an aim. This study finds rates of progressive dwindling in PwMS far greater than in the general population. Progressive dwindling can be predicted in PwMS by early markers of aggressive disease, and is not associated with a different place of death.*

   We agree. We have deleted this from the introduction and have not inserted it elsewhere since it is already described in the results and discussion.

8. *Material and methods. More on setting. Tell us more about the MS Tissue Bank and why this was a reasonable repository of data to examine. How many individuals are included within this bank? How complete is it/representative is it, of the MS population. Time frame for study is essential .*

   We have improved the methodology to describe more precisely the UKMSTB. The time frame has been added: "all those people with MS that died between January 1998 and February 2015 inclusive (n=606)". Of these 606, 9 were excluded because MS was not confirmed on post-mortem tissue diagnosis, and 15 were excluded due to insufficient data on cause of death, leaving the cohort of n=582. The strengths of the UKMSTB are now described in the discussion: "The UKMSTB is a community based scheme where people with MS register during their lifetime for tissue and clinical data to be collected when they die. Donors are representative of MS patients nationwide as a result of a national community-based recruitment strategy, with accurate representation of clinical milestones and MS sub-types confirmed by comparison with other study populations. One advantage of this large cohort of 582 pwMS is that extensive clinical summaries are available for each donor, to allow accurate categorisation of disease milestones, trajectories, and cause of death. In addition, it was possible to include cases regardless of whether MS was mentioned on the death certificate, in contrast to previous studies on mortality in MS. Indeed, in our cohort, MS was not mentioned on the death certificate in 35.9% of cases, many of which we adjudged to have died an MS-related death after inspection of clinical records. Furthermore, by manually categorising UCD in each patient, we mitigated the effect of heterogeneous death certification technique and coding rule changes which can lead to inconsistent reporting of UCD within other studies."

9. *More information on how well clinical notes were triangulated with death registration data. Was this done for all deaths or just a selected number. What changes if any were made after consulting clinical notes as there are known vagaries with death certificates*

   Thank you for the comment. Clinical notes were reviewed in all patients, and this has now been stated in the methodology. We now state: "Clinical notes were used to define the date of symptom onset, progressive disease (defined as a period of at least one year with gradual disability worsening without relapses), wheelchair use, and death, for all patients."

   We also now explain "Death certificate entries were used to categorise underlying cause of death (UCD), and confirmed using patient notes and

clinical summaries when the death certificate was unclear. For example, if the death certificate stated 'infection' or 'respiratory failure', clinical notes were used to identify a more specific UCD e.g. pneumonia. If multiple causes were listed on the death certificate, clinical notes were used to discern the primary cause of death." Various scenarios are discussed in the methodology, to explain how cause of death was coded if there were discrepancies between the death certificate and clinical notes.

10. *Not necessary to include ... Requests for data can be made to the UK MS Tissue Bank via Dr Richard Nicholas (r.nicholas@imperial.ac.uk).*

This has now been removed.

11. *Statistical analysis is adequate but please be much much clearer in what ways the analysis follows or addresses the study aims/objectives. X was done in order to examine…. Y and so on.*

We believe that this section has been improved, it now states: Cox proportional hazards regression was performed to compare survival from disease milestones between different groups e.g. those with MS-related deaths vs. those with non-MS-related deaths, those who progressively dwindled vs. those with other disease trajectories. Disease milestones were compared between all four disease trajectory groups using one way between subject ANOVA, with Tukey HSD used post hoc for significant ANOVA analyses. Student's t-test was used to compare demographics in males and females. Parametric tests were performed after testing for normality. Chi-squared test was used to compare location of death in those with different trajectories to death, and those with and without MS-related deaths. Yates' chi-squared test was used to avoid overestimation of statistical significance. Where chi-squared revealed significance in contingency tables greater than 2x2, further post hoc 2x2 chi-squared tests were carried out to identify the significant values, with criteria for statistical significance adjusted according to the number of post hoc tests carried out.

12. *Table 1 useful but please include timeframe.*

The timeframe (Jan 1998 to Feb 2015) has been added - thanks.

13. *Page 9-10. How exactly was progression calculated? This is really important and omitted Did the authors make use of the multiple sclerosis severity score (MSSS) or the progression index (PI). This is not clear from the information provided.*

Progression was defined as "a period of at least one year with gradual disability worsening without relapses" – this has been added to the methodology. The date of progression was extracted from clinical notes in all cases by the senior author of this manuscript – a neurology consultant who specialises in MS. MSSS and PI were not used in this study.

14. *Title for section that commences page 13 needs to be changed to location of death. Give proportion of death that have known location of death please. What exactly is community? This is a very diffuse term and needs to be clarified. Percentages would be useful rather than just the n's.*

The title of the section has been changed. Location of death was known in 86.4% of subjects – this has been added. Community is defined as "Own residence, care home and hospice deaths" – this was already stated in the methodology, but has now been added to Table 3. Percentages have also been added to the tables.

15. *Page 14: Of course we have no idea where these patients wanted to die. This must be discussed later on.*

This is an important point, and has now been mentioned in the discussion.

16. *Please change opening to discussion. Good to hear it is the first study but bolster it up by telling us why this is important too.*

The opening paragraph of the discussion has been rewritten, and now summarises the main study results, and why these are important. We hope you consider it an improvement.

17. *Back to completeness of the UKMSTB. Please remind us hjow many people with MS are included and this may be a big strength of your study.*

The completeness of data in the UKMSTB is one of the major strengths of this study. We have improved the discussion of this: ""The UKMSTB is a community based scheme where people with MS register during their lifetime for tissue and clinical data to be collected when they die. Donors are representative of MS patients nationwide as a result of a national community-based recruitment strategy, with accurate representation of clinical milestones and MS sub-types confirmed by comparison with other study populations. One advantage of this large cohort of 582 pwMS is that extensive clinical summaries are available for each donor, to allow accurate categorisation of disease milestones, trajectories, and cause of death. In addition, it was possible to include cases regardless of whether MS was mentioned on the death certificate, in contrast to previous studies on mortality in MS. Indeed, in our cohort, MS was not mentioned on the death certificate in 35.9% of cases, many of which we adjudged to have died an MS-related death after inspection of clinical records. Furthermore, by manually categorising UCD in each patient, we mitigated the effect of heterogeneous death certification technique and coding rule changes which can lead to inconsistent reporting of UCD within other studies.""

18. *Would be very useful to refer to Murtagh et al How many people need palliative care? A study developing and comparing methods for population-based estimates Palliat Med. 2014 Jan;28(1):49-58. doi: 10.1177/0269216313489367. Epub 2013 May 21 to strengthen you discussion.*

The above studies have now been discussed and referenced – we agree this strengthens the discussion.

19. *Study limitations please. Please examine them in relation to the inferences we can take away from the data you provide.*

An additional paragraph has been added about study limitations: "The most important limitation of this study was that data were retrospectively collated from clinical records and notes. The required data was not apparent on occasion, for example the 'date of wheelchair use' may not have been documented, while on other occasions coding of data required

interpretation by the assessor. However, care was taken to formulate standardised rules for coding, and the availability of clinical notes improved reliability of data over death certificates. Overall, manual determination of these factors was considered to be a strength of this study as it allowed a more thorough analysis of each case, using the clinical summary where necessary. Another possible limitation is that cases were included whose deaths occurred between 1998 and 2015. Standards of care may have changed over this period, although the results reported in this study appeared consistent over time."

20. *Conclusion takes quite a while to get to the message central to this paper i.e. people with MS. Commence with. We have shown that progressive dwindling is even more common in MS. Also no absolutely no mention of place of care or death here. If this is a central message of the paper it needs to be focused on here too. How can formative care lead to achieving preferences for location of care, death and more patient and family centred care. Family never mentioned. Why not?*

The conclusion has been largely rewritten to better reflect the findings of the study, and to summarise the central message. We have now mentioned the family and carers at several points in the introduction, discussion, and conclusion – thank you for pointing out this omission. We hope that the reviewer thinks the new conclusion is an improvement.

Reviewer: 2
Comments to the Authors:
Thank you for asking me to review this very interesting manuscript on progressive dwindling in MS. Overall I think this is an excellent piece of paper and of relevance to those working in the field of MS. The method is clearly presented and the results and implications are well described.

Thank you for these comments.

Minor comments:

1. *There is a research group in the UK testing efficacy of Palliative Care (PC) services for people with MS or any neurological condition. See publications from Irene Higginson et al. on their fast-track palliative care trial. In Germany, there is a research group analysing (palliative care) needs of MS patients and when and how to integrate PC into the disease trajectories (see for instance Golla et al, Strupp et al. Galushko et al). It would be good to cite some of their work, perhaps insert information in the discussion section where you already mention the Italian research group. Since you mention that formative care is also inclusion of PC, citing more literature in the discussion could add value to your work.*

The above studies have now been discussed and referenced – we agree this strengthens the discussion – thank you.

2. *Table 1: Pneumonia, bronchopneumonia 218 (37.4), in the text it says 37.5 %. Please correct accordingly. All in all a very fine piece of work!*

This has now been amended to 37.5% – thank you for noticing this error.

We thank the editor and the reviewers again for their time, and for considering this manuscript.