Nutrition Research

A cross sectional assessment of nutrient intake and the association of the inflammatory properties of nutrients and foods with symptom severity, in a large cohort from the UK Multiple Sclerosis Registry.

--Manuscript Draft--

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Abstract:	To assess the intake of nutrients in people with Multiple Sclerosis (pwMS) compared to a control population, and to assess the pro/ anti-inflammatory properties of nutrients/ foods and their relationships with fatigue and quality of life. This was a cross sectional study in which 2410 pwMS (686 men; 1721 women, 3 n/a, mean age 53 (11 yrs)) provided dietary data using a Food Frequency Questionnaire that was hosted on the MS Register for a period of three months and this was compared to a cohort of 24,852 controls (11,250 male, 13,602 female, mean age 59 yrs). Consent was implied by anonymously filling out the questionnaire. A Wilcoxon test was used to compare intake between pwMS and controls, and a bivariate analyses followed by chi 2 test were undertaken to identify significance and the strength of the relationship between pro/ anti-inflammatory dietary factors and fatigue and EQ-5D. Compared to controls, all nutrients were significantly lower in the MS group ($p<0.05$). Bivariate associations showed a significant correlation between consuming fish and lower clinical fatigue ($\chi2(1) = 4.221$, $p <0.05$), with a very low association (φ (phi) = -0.051, p=0.04. Positive health outcomes on the EQ-5D measures were associated with higher carotene, magnesium oily fish and fruits and vegetable and sodium consumption ($p<0.05$). Fibre, red meat and saturated fat (women only) consumption was associated with worse outcomes on the EQ-5D measures ($p<0.05$). People with MS have different dietary intakes compared to controls, and this may be associated with worse symptoms.
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Response to Reviewers:	

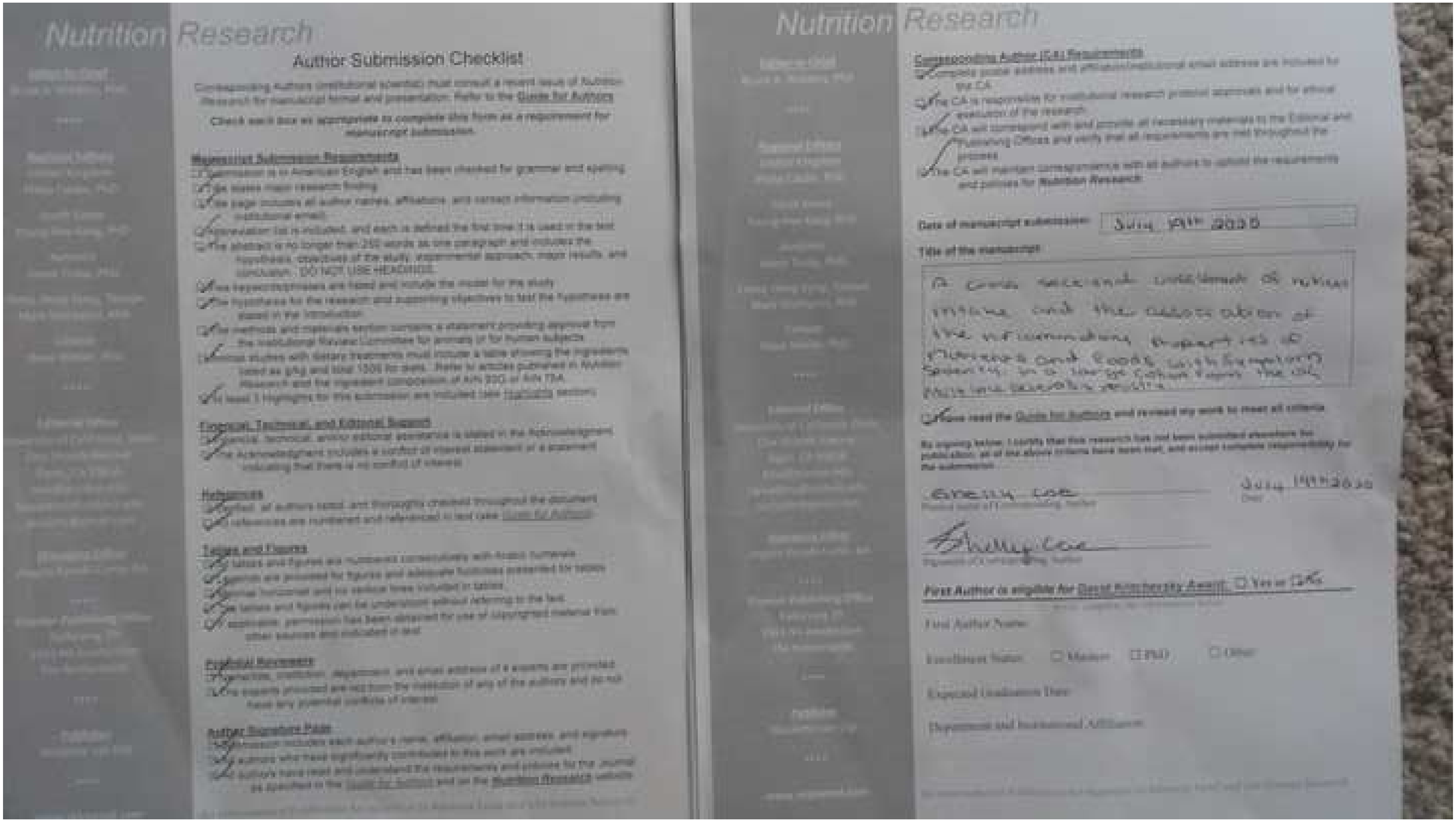
To whom it may concern

Attached is our proposed submission for **Nutrition Research**. We as the authors feel that the current paper fits with the aims and scope of the journal, and we hope that you consider the paper for submission. All authors agree to this submission, and confirm that this work has not been published elsewhere. The manuscript does not contain experiments using animals. This has been a journal that we have read and respect, and we would feel privileged to be considered for such a publication in this journal. As far as we are aware, we have complied with the journal requirements and have attached all necessary information. We also declare no reason that our paper should not be accepted into the journal.

I am happy to discuss any issues as the corresponding author, and I look forward to hearing your comments on the original paper.

Thank you and regards,
Dr Shelly Coe

Checklist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Other
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The authors would like to thank the reviewers for their extensive feedback and thorough investigation of the paper and its results. We believe the feedback has helped to improve the quality of the paper, and we have addressed each point below. We do hope the manuscript is now suitable for publication, however if there is anything else we can do to improve the manuscript we would be happy to make any further changes.

We believe the comments from the first set of reviewers 1 and 2 were by mistake as we did not report any data about type 1 diabetes and the comments do not match with this current paper. However if we have made a mistake please let us know.

With many thanks
Shelly Coe

Reviewer #1

1. Intro: maybe worth mentioning the numerous dietary strategies that are being used by many people with pwMS already and how this study may challenge or strengthen some of this information.

Response: Thank you for the suggestion, a sentence has now been added in the introduction as follows: There are various diets that are followed by pwMS including the low saturated fat Swank diet and the Wahls Palaeolithic diet [7] and pwMS also tend to have a high consumption of herbs and supplements [8]; [8]; however the effect of these diet practices on nutrient intake and nutritional status in pwMS is not known.

2. Discussion: Although the health benefits of consuming fish products were discussed it might also be worth commenting on studies that have focused on other omega fatty acid-rich oil such as flaxseed oil and algae oil (if any studies on this oil). Did any participants consume any of these oils? Were there any other specific or interesting details found from the food frequency questionnaires?

Response: This is a very interesting point and we would like to thank the reviewer for taking the time to provide important feedback from the discussion section. After a search of the literature, there is no strong evidence on flaxseed nor on algae for providing benefits to pwMS. However, as a small amount of people did consume flaxseed oil in the current study, I have added the following to the discussion:

Line 360: It was shown that the 72 people (0.03%) in the current study consumed flaxseed oil which is an alternative source of omega-3.

Reviewer #2

1. the comparison with normal population regards guidelines produces in the period 1993-1997; patients were investigated in 2016; did it change any diet habit in UK population?

Response: The authors would like to thank reviewer 2 for their comment. The control paper did report data from an earlier time period, however it used the same food questionnaire and it covered 25,000 people which is more than any other study using the EPIC could provide. Although certain diet government guidelines have changed slightly over this time period, the changes are minor and therefore would not have largely impacted the results from the food questionnaire. Some changes would have occurred due to food composition changes and others due to health messages, for example a decrease in fat and sodium and an increase in fruit and vegetables, however these changes would not be large enough to cause worry in the results (Prynne et al 2005).

The above phrase has now been added to the discussion under the limitations section, line 409.

2. the authors studied patients of white race, over 90% of participants; was it the same percentage of control data?

Response: The control paper did not report these demographics and therefore unfortunately we can not comment on this. However age and gender ratio were similar between our study and the control paper.

Our paper, gender: 71 % female, age: 53
Control paper, gender: 55% female, age: 59

The following sentence has been added to line 214 in the discussion:

Gender and age ratios were similar between this cohort and the control data (71 % female, age: 53 vs control paper, gender: 55% female, age: 59).

3. the authors investigated diet habits in 38.6% of pwMS who were employed; again, was it the same the percentage of employed persons among control data?

Response: The control paper did not report these demographics and therefore we cannot comment. The Office for National Statistics reports that 76.6% of UK adults are employed. However age and gender ratio were similar between our study and the control paper. The following sentence has now been added to the discussion under limitations:

Line 418: Also, employment and race were not reported in the control paper, and therefore this information could not be compared across the cohorts.

4. there is some confusion information about the percentage of participants; it was reported that register users are 16,000; but the percentage is calculated on 10,000

Response: Thank you for this feedback. There are currently 16000 actively engaged people on the register, however at the time of our data collection there were 10,000. Therefore I have made this distinction clear in the current paper as follows:

Line 219. At the time that the questionnaire was hosted on the register, 10,000 users were registered with 4,000 of these users actively engaged in the register during any three month period.

5. it appears that questionnaires and other information about the disease was completed by patients; is it correct? On these grounds, the question is: which was the accuracy of information provided by patients and not controlled by doctors? do the authors have further data about a possible control of self provided information compared with information obtained by a doctor lead interview?

Response: The reviewer makes a valid point that data was self reported and therefore the lack of a clinical confirmation is a limitation to the current study. However considering the large amount of people with MS that we could access via the MS Register compared to via through clinics, this was unavoidable as people who sign up to the register self confirm their diagnosis.

The Register clearly states that you must have Multiple Sclerosis in order to sign up and complete the questionnaires. Self report data is common practice amongst large cohort data sets for diet research (Martínez-González et al 2008, doi: https://doi.org/10.1136/bmj.39561.501007.BE). Also, patient self reported data in other health conditions has shown to be highly correlated to clinician reported data, and therefore we expect this to extrapolate to MS (Ye at al 2017, doi:10.1001/jamaoncol.2016.6744, Kilbourne et al 2017, https://doi.org/10.1089/jwh.2016.6069).

6. regarding EQ 3L: generally when we have 3 points or 5 points, people are more prone to stay in the middle, 2 or 3. Which was the percentage of pwMS self rating 2 or 3?

Response: Thank you. The authors did not use the EQ 3L questionnaire and therefore we can not comment on this statistic. However we did use the EQ-5D, and the average score was 3 out of 5 for respondents, with 18.7% reporting a 3.

7. I expected to have further analysis, more neurological, for instance the impact of disease phenotype, disease duration etc.

Response: The authors would like to thank the reviewer for his or her comments. Although we agree that this further analysis would be interesting, there was a lot of data in the current paper and therefore we had to limit the results that were reported based on the main aims of the paper. Because duration of disease can vary greatly from first symptom to an actual diagnosis, we concluded that for this paper it was not the most important demographic to assess. We did report the different types of MS in table 1, however because 50% of all people reported having RRMS, we did not think appropriate to further analyse this. If this is something that the reviewer would like us to add to the paper, and therefore is not happy with our response, then we will consider adding more data to the paper.

8. I expected to have further analysis investigating the impact of employment.

Response: Due to a lack of reporting on employment in the control paper, we could not compare. Due to a large amount of people reporting 'other' for employment, we could not further analyse this in our paper.

9. Again, I expected to have further analysis investigating the difference among races.

Response: Due to a lack of reporting on race in the control paper, we could not compare. Because 90% of our population was white, we did not think it appropriate to further explore this with our data.

10. Rephrase the sentence at line 232 Negative correlations.

Response: this has now been rephrased as follows: A negative correlation was found between sodium intake and usual activities (r=-0.044, p=0.035).

11. I am not so sure to use the adjective common for bowel incontinence in pwMS.

Response: The word ‘common’ has been removed.

12. Maybe, in discussion it could be useful to cite the research investigating frankincense extracts as possible DMD.

Response: The authors agree that the literature around frankincense and therapeutic treatment for RRMS is compelling and indeed an important addition to the field (Hanja Stürner et al., 2018); however as none of the participants in the current study consumed this and because the paper is already very long with a lengthy discussion section we have decided not to include in this specific paper.

Highlights

1. People with MS have different diets than the general population, which could lead to deficiencies in some key nutrients

2. Certain nutrients/ foods are associated with worsening symptoms including fatigue and quality of life measures.

3. Improving diet in pwMS may improve symptom severity and overall quality of life

A cross sectional assessment of nutrient intake and the association of the inflammatory properties of nutrients and foods with symptom severity, in a large cohort from the UK Multiple Sclerosis Registry.

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Abstract

To assess the intake of nutrients in people with Multiple Sclerosis (pwMS) compared to a control population, and to assess the pro/ anti-inflammatory properties of nutrients/ foods and their relationships with fatigue and quality of life. This was a cross sectional study in which 2410 pwMS (686 men; 1721 women, 3 n/a, mean age 53 (11 yrs)) provided dietary data using a Food Frequency Questionnaire that was hosted on the MS Register for a period of three months and this was compared to a cohort of 24,852 controls (11,250 male, 13,602 female, mean age 59 yrs). Consent was implied by anonymously filling out the questionnaire. A Wilcoxon test was used to compare intake between pwMS and controls, and a bivariate analyses followed by chi^2 test were undertaken to identify significance and the strength of the relationship between pro/ anti-inflammatory dietary factors and fatigue and EQ-5D. Compared to controls, all nutrients were significantly lower in the MS group ($p<0.05$). Bivariate associations showed a significant correlation between consuming fish and lower clinical fatigue ($\chi2(1) = 4.221$, $p <0.05$), with a very low association (φ (phi) = -0.051, p=0.04. Positive health outcomes on the EQ-5D measures were associated with higher carotene, magnesium oily fish and fruits and vegetable and sodium consumption ($p<0.05$). Fibre, red meat and saturated fat (women only) consumption was associated with worse outcomes on the EQ-5D measures ($p<0.05$). People with MS have different dietary intakes compared to controls, and this may be associated with worse symptoms.

Key words: Diet, Multiple Sclerosis, fatigue, inflammation, quality of life

Abbreviations

FSS, fatigue severity scale; FFQ, food frequency questionnaire; HRQOL, health related quality of life; pwMS, people with Multiple Sclerosis; SACN, Scientific Advisory Committee on Nutrition

1. Introduction

Research has indicated that there is a higher incidence of MS in Western countries where diets are typically high in calories and saturated fatty acids, low in polyunsaturated fatty acids and vitamin D [1]. However, although an emerging area, there are few studies which analyse the dietary habits of people with MS (pwMS), and likewise there are few studies which correlate these dietary habits with validated health outcomes [2] [3] [4] [5].

Considering that MS is increasingly diagnosed earlier in life [6], an understanding of the nutritional implications of what pwMS consume is an important area to understand and consider in clinical advice and when considering dietary interventions for trials. There are various diets that are followed by pwMS including the low saturated fat Swank diet and the Wahls Palaeolithic diet [7] and pwMS also tend to have a high consumption of herbs and supplements [8]; however the effect of these diet practices on nutrient intake and nutritional status in pwMS is not known.

Indeed pwMS have been shown to have altered nutritional intake patterns compared to reference nutrient intake guidelines [9]. From a pilot study in 31 pwMS, [10] it was also found in a small study of pwMS that they did not meet UK Government diet guidelines. From this small study missing data was low and response rate was high with participants indicating that they were interested in dietary approaches to manage their condition and symptoms.

Studies also suggest that healthy dietary patterns and supplement use can reduce cytokine production and therefore reduce inflammation [11] improve fatigue, body mass index (BMI), low-density lipoprotein cholesterol, total cholesterol and insulin [12] in pwMS. To date limited research has explored pro/ anti-inflammatory food types in MS.

Thus, the aim of this study was initially to assess the diet quality and supplement intake of pwMS and to compare nutrient intake to a general population sample. Aspects of feasibility were explored to estimate how many and the profile of people on the Register who completed dietary information and completion of measures. This study also aimed to explore associations between intake of individual food and nutrients, and the extent and direction of the relationship of pro and anti-inflammatory food, as determined from the literature, on health related quality of life and fatigue.

2. Methods and Materials

This was a cross sectional study between October 2016 to December 2016 including 2410 people with MS (686 men; 1721 women, 3 n/a, mean age 53 (11) yrs) and 24852 controls (11250 male, 13602 female, mean age 59 yrs). Control data was taken from a previous study [13] from an East England population collected between 1993 and 1997 using the same food frequency questionnaire (FFQ). The sample represented the ‘standard’ population. Participants with MS were registered on the UK Multiple Sclerosis (MS) Register and had consented to being over the 18 years of age with a diagnosis of MS. The MS Register has approximately 16,000 current users. Registered individuals received information about the study on the Register and were informed through email once the questionnaire had been uploaded. Consent to the study was implied through the completion of anonymised questionnaires. Ethical approval for this study was granted by the Oxford Brookes University Ethics Committee (150895). Control data was taken from [13].

2.1 Measurements

The EPIC-Norfolk Food Frequency Questionnaire (FFQ) [14] was hosted on the MS Register for a period of 3 months. It was used to measure habitual food intake over the previous 12 months and took approximately 30 minutes to complete. It included questions about specific food items, such as seasonal consumption of fruit and vegetables and habitual consumption of meat, fish, dairy products, potatoes, breads, rice, fats and sugars. Answers range from 'never or less than a month' to '6 + times a day'. In addition, participants were also asked whether they took nutritional supplements and asked questions regarding their cooking methods, including the use of oils and added salt. The FFQ was analysed using software from the European Prospective Investigation into Cancer (EPIC-Norfolk) Cohort study [14] from which the accuracy of the analysis was originally validated. Through this software, whole foods are converted to total macro and micro nutrients consumed over the previous year in amounts. Questionnaires with more than 10 ticks missing were excluded from the analysis [15]

The Fatigue Severity Scale (FSS) was used to measure fatigue [16]. Those who were fatigued as indicated by a score of 4 or more on the FSS were then compared to those who were non fatigued (FSS <4).

The questionnaire packs took an average of 30 minutes to complete. Demographic information was collected including weight, height, gender, date of birth and Barthel Index Activities of Daily Living [17] and was also self-reported.

The EQ-5D (Appendix D) was used to measure health related quality of life (HRQOL). Participants rated their severity for each question using a three-level (EQ-5D-3L) scale with 1 indicating no difficulty, 2 indicating moderate difficulty and 3 indicating severe difficulty. An overall health score was provided to participants who answered all five of the EQ-5D questions, with a 0 being given to participants who recorded no difficulty, and a 1 being given to participants who reported either moderate or severe difficulty. As such the minimum score was 0 and the maximum 5, with the latter being the worst health state. Participants also evaluated their health status using the visual analogue scale (EQ-VAS) which is numbered from 0-100 with 100 being the best health status.

2.2 Outcomes

The feasibility aspects of the study were determined through the efficiency of data collection methods through completion of the questionnaires, identification of missing data and recruitment rate. Questionnaires with less than 500 kcal or more than 3500 kcal were excluded from the analysis [18].

Anti-inflammatory nutrients/ food groups namely carotene, magnesium, oily fish and fruit and vegetables, and pro inflammatory nutrients/ food groups including saturated fat, sodium, sucrose, red meat and high-fat dairy products, were looked at for associations with fatigue and HRQOL.

Intake of saturated fat, sodium and sucrose of participants were directly comparable to UK dietary guidelines from the Scientific Advisory Committee on Nutrition (SACN). In order to achieve a participants total intake of unprocessed and processed red meat the following foods were combined: beef, burgers, pork, lamb, bacon, ham, corned beef, and sausages. The Food Frequency Questionnaire (FFQ) asked for the frequency of consumption in terms of 'medium portion sizes.' In order to compare participants intake of red meat to the UK dietary guidelines from the SACN who provides recommendations for such in terms of grams, it was necessary to convert participants intake from 'medium portion sizes' to grams. Standard conversions from 'medium portion size' to grams were obtained from EPIC-Norfolk. Daily intake of one of the red meat components could therefore be calculated using the following calculation:

Portion size in grams / frequency of consumption = total daily intake. For example, a medium portion size of beef equated to 116g and if a participant consumed beef once a week the following calculation was performed: 116g / 7 = 16.5g of beef daily. This method was repeated for the remaining red meat components. The combined sum of all components provided the total amount of red meat consumed daily. Currently the SACN recommend that a daily consumption of 90g of red meat be reduced to 70g, hence, 70g was used as the recommended intake for both men and women.

In order to compute a participants total intake of high-fat dairy products the following foods were combined: single/soured cream, double/clotted cream, full fat/Greek yogurt, dairy desserts, cheese and full cream milk. For dairy products the FFQ either provided the participant with a gram amount of a product, or stated a ‘medium portion size’. If it was the latter, the same conversion method described for red meat was used to obtain a participants daily intake. As there are currently no dietary guidelines relating specifically to the intake of high-fat dairy products, no comparisons could be made.

One point was awarded for meeting or exceeding the recommended intake for each dietary factor. The total score ranged from 0-4 where 0= Did not meet any of the recommendations and 4= Met all of the recommendations. Each item was given equal weighting for ease.

2.3 Statistical analyses

Demographic data was described using descriptive analysis and response rate was estimated. Completeness of questionnaires was reported and 80% was considered appropriate for each measure including demographic information. Significance level was set at 5% with 95% confidence intervals. Multicollinearity was assessed and collinear variables were not included. Data were analysed using SPSS Statistics Version 25 (IBM SPSS Statistics for Windows, IBM Corp, Armonk, NY, USA). Independent t tests for males and females were performed to compare mean values for each nutrient to the UK guideline recommendation for these nutrients.

Bivariate analysis were undertaken to explore associations between intake of pro and anti-inflammatory nutrients/food items and fatigue and EQ-5D measures of health. Spearman product-moment correlations and (2x2) chi-square tests of association were used to assess the direction and strength of the relationship between variables. Low, medium and high correlation coefficients were considered as 0.3 to <0.5, 0.5 to <0.7 and 0.7 to<0.9 respectively. All expected cell frequencies were greater than five. For all tests, two-tailed tests of significance were used with alpha (α) level set at 0.05.

3. **Results**

Demographic information is shown in table 1 and a breakdown of types of supplements used in this population are shown in table 2. Gender and age ratios were similar between this cohort and the control data (71 % female, age: 53 vs ontrol paper, gender: 55% female, age: 59). As shown in table 3, nutrients were found to be significantly different between the MS cohort and the controls when divided into men and women (p<0.05). PwMS consumed less of all nutrients compared to the control data set.

At the time that the questionnaire was hosted on the register, 10,000 users were registered with 4,000 of these users actively engaged in the register during any three month period. The use of the register therefore allowed us to collect a large amount of data in a very distinct subset of the population in a short period of time. With a response rate of 2,495 this equates to over a 60% response rate. A total of 2410 questionnaires were used in the final analysis, which composed of missing data (approx. 45 questionnaires) or outliers (approx. 40 questionnaires) and therefore missing data was less than 2%. There was a statistically significant association between consuming fish products (>40g/day) and clinical fatigue ($\chi^2(1) = 4.221$, $p < 0.05$, table 4), with a very low association (φ (phi) = -0.051, p=0.04. Positive correlations (albeit weak) were found between pain (r=0.041, p=0.048), anxiety/ depression (r=0.06, p=0.04) and red meat intake (table 5).

A positive correlation was also observed between anxiety and saturated fat intake in women (r=0.055, p=0.026). A negative correlation was found between sodium intake and usual activities (r=-0.044, p=0.035).

Those who met or exceeded the recommended intake of carotene rated their overall health state higher (r=0.071, p=0.001). Consuming the recommended daily amount of fruit and vegetables was also significantly associated with better self care (r=-0.044, p=0.035), better overall health state (r=0.071, p=0.001) and less anxiety and depression (r=-0.048, p=0.022). Consuming oily fish once per week or more was significantly associated with better anxiety and depression (r=-0.057, p=0.006) and mobility (r=-0.047, p=0.023). Magnesium associated with a better score for usual activities (r=-0.048, p=0.021) and a higher health state (r=0.045, p=0.03). All correlations were weak.

However, those who consumed the recommended daily amount of fibre were significantly more likely to have self care related problems (r=0.051, p=0.013), pain (r=0.049, 0.018), and problems carrying out usual activities (r=0.062, p=0.003), and significantly less likely to have a better health state (r=-0.041, p=0.046). Overall only

45 out of the total cohort consumed at or above the recommended 30 grams of fibre a day.

4. **Discussion**

We found that pwMS consumed less nutrients, high levels of supplements and that participants with better diet quality had lower levels of disability except for a few notable food groups. Finally there was a relationship of anti-inflammatory foods to improved fatigue and HRQOL. Considering the strong relationship of fatigue to poor health and our observations, our findings suggest that diet could be an important approach to influence symptoms, health and wellbeing in pwMS.

4.1 Comparison of food intake to the general public

PwMS consumed less nutrients based on the EPIC questionnaire, compared to a control population. A previous pilot study from our lab compared the dietary patterns in pwMS compared to the UK guidelines, and found pwMS tended to have insufficient intakes of many ‘healthy’ nutrients compared to the UK guidelines, and pwMS who are fatigued have even lower intakes of certain nutrients compared to those who are non-fatigued. Notable differences were found in those with more severe fatigue and in men who generally had a poorer diet[10]. Compared to the current study, the only other similar study to date was that by [4] who performed a cross sectional study in 101 Relapsing and Remitting MS participants. Diet was assessed using a 3 day food diary and it was found that intake of vitamin D, folate, calcium and magnesium were lower in pwMS compared to the recommended Dietary Reference Intakes, and lower dietary intake of magnesium and folate correlated with higher fatigue scores. Therefore, they suggested that correcting intake of these dietary components may improve fatigue levels in pwMS,

4.2 Supplements

Among the supplements consumed, Vitamin D and Omega 3 were the most common in this cohort. Interestingly approximately a third of pwMS have previously reported using complementary alternative medicine including supplementation in conjunction with conventional therapies to try to alleviate such symptoms and reduce disease progression [19]. A recent systematic review on Vitamin D and symptom severity in pwMS found improvements in symptoms in those in the Vitamin D trial arm, however these improvements were more apparent in those with lower baseline plasma levels. Results from this study showed favourable effects of higher oily fish consumption and improvements in various symptoms. Therefore consumption of Omega 3 may further improve these results. However NICE currently does not suggest Omega 3 or Vitamin D supplements for pwMS due to the lack of research showing positive effects and therefore this is an area that need further investigation

4.3 Diet and symptom severity

A similar patient registry, the North American Research Committee of Multiple Sclerosis (NARCOMS), which was founded in 1993, has also shed light on the many associations between diet quality and disability and symptom severity in pwMS. In a survey of almost 7000 participants from the NARCOMS register, diet quality scores were compared with disability status and symptom severity. It found that participants in the highest quintile for diet quality had lower levels of disability and in terms of food groups, individuals in the top quintile for whole grain intake and total dairy were less likely to have a severe disability than those in the bottom quintile of each food group [5]

High red meat consumption was associated with worse fatigue, more pain and worse anxiety and depression. Red meat is a source of arachidonic acid, the omega-6 polyunsaturated fat which is pro-inflammatory. Red meat also contains more iron heme than in comparison to white meat and iron deposits have been located at the sites of inflammation in pwMS. Consumption of red meat is also associated with higher levels of the C-reactive protein ; a marker of inflammation[20].

There were no positive significant correlations between sodium intake and any of the outcome variables. However, usual activities were improved in participants who exceeded the recommended intake of 1600mg/day. These results contradict findings from Farez et al [21] who conducted an observational study in 70 people with RRMS and found increased sodium intake was significantly correlated with the exacerbation of pre-existing symptoms. Although it is difficult to make direct comparisons given the difference in outcome measures, the discrepancies between this study and the one conducted by Farez et al [21] could be due to the different methods of measuring sodium intake. Farez et al [21] estimated sodium intake via sodium excretion in urine samples which is considered to be the ‘gold standard’ of estimating sodium intake whereas this study used a FFQ.

Meeting or exceeding the recommended total carotene intake was associated with a better overall health state. The antioxidant properties of carotenoids are well known [22], but in addition they are precursors to vitamin A which has been shown in studies to suppress the formation of pathogenic T cells and increase the formation of regulatory T cells in pwMS [23]. In a recent randomized controlled study, RRMS participants were supplemented with 25000 IU/day of vitamin A for six months and

10,000 IU/d for an additional six months. The results showed a significant decrease in the progression of upper limb and cognitive disability, but EDSS, relapse rate and brain active lesions did not change[24].

The relationship found in the present study between higher fruit and vegetable intake and better self-care , less anxiety and depression and better health state is in agreement with Hadgkiss et al., [3] who found that people who had a ‘healthy’ fruit and vegetable sub score reported having better mental health and health. Whether it is the direct effect of antioxidants or the secondary effects of fibre in fruit and vegetables that enable a more stable and symbiotic gut microbiome, is unknown, but both mechanisms can possibly reduce inflammation [20]. Also a causation relationship can not be confirmed, as people who feel better in the physical and mental state may also take up more healthy lifestyle behaviours such as increasing fruit and vegetable consumption. Emerging research is beginning to link inflammation that originates in the gut microbiome to poorer mental health [25]. Surprisingly, several positive correlations were found between fibre intake and aspects of the EQ5D questionnaire indicating that high intakes of fibre were associated with more severe health problems. One possible explanation for this could be when health starts to deteriorate as a result of MS, people start to make improvements to their diet including increasing fibre consumption. Also overall fibre intake in the cohort was low which could impact on the findings, and could be a results of lower recommendation of 18g that was in existence during the timeframe that the data was collected. Alternatively, participants may have been deliberately limiting their fibre intake for fear of exacerbating bowel incontinence which is a problem among pwMS [26].

The results support the original hypotheses that pwMS who consume fish are less likely to experience clinical fatigue and are more likely to report a better perceived health state and fewer health problems associated with MS, and are in concordance with other studies [27-30]. Omega-3 has anti-inflammatory, antithrombotic and immune-modulatory capabilities and is able to inhibit the synthesis of proinflammatory eicosanoids [31]. It was shown that the 72 people in the current study consumed flaxseed oil which alternative sources of omega-3.

Overall, only a limited number of the results achieved were significant. This is not surprising as diet is one of a number of modifiable factors that also should be considered, and in the context of an individual's environment and socio-economic status. The possibility of reverse causality cannot be ignored and it is feasible that increased disability could lead to a diet lower in anti-inflammatory and higher in pro-inflammatory factors rather than the obverse. Coe et al [32] found that a high flavonoid cocoa beverage showed promise for improving fatigue and fatigability, in addition to other mental and physical health measures and the anti-inflammatory properties of flavonoids was proposed to be one of the mechanisms for this. It is likely that pwMS with deteriorating health may be less likely to persist with healthy lifestyle behaviours such as 'healthy' eating and therefore more likely to opt for 'unhealthy' food [33]. This is a feasible explanation given how increased disability may affect an individual's ability to cook and therefore lead to the increased consumption of processed meals which are energy dense and high in saturated fat and sodium. Although there are many complementary therapies and pharmacological interventions aimed at combatting fatigue [28], with the exception of exercise, none specifically target inflammation. Therefore we suggest that a diet rich in anti-inflammatory promoting nutrients and food will contribute to the alleviation of fatigue and in turn improve quality of life for pwMS.

4.4 *Strengths and limitations*

The main strength of the study was its large sample size including people with all types of MS and males were also well represented. In addition, a recent comparison of the UK MS Register portal population with the clinical population found them to be closely matched for mean age at diagnosis and gender ratio. It also supports the validity of the self-reported MS diagnoses as it was found to be highly analogous to the clinical population [34]. The main strength of using a FFQ to collect dietary data is its ability to assess long-term dietary intakes in a relatively simple, cost effective and time-efficient manner. Nutrient intakes estimated using the EPIC FFQ have been validated against weighed records and the correlation coefficients were generally of the order of 0.4-0.6. These correlations were similar to values obtained elsewhere in comparative validation studies [35]. Survey participation was anonymous which reduces the chances of responder bias.

However, nutritional status cannot necessarily be gauged by intake due to bioavailability and nutrient absorption. FFQ’s rely heavily on recall accuracy and it is estimated that recall methods of dietary analysis underestimate dietary analysis by 10% when compared to observed intake [36]. When completing FFQ’s participants are said to under report food intake in an attempt to portray a ‘healthier’ diet [14] however, this study minimised this risk by the use of anonymous questionnaires. People with little interest in diet as a complimentary therapy may have been less likely to participate in the study and those who did may have reported healthier dietary habits than that of reality. There was also a limited amount of demographic information meaning that it was impossible to account for other possible confounders such as BMI. The inclusion criteria also did not omit smokers or participants with co-morbidities such as high cholesterol all of which could have confounded the results achieved. The use of web based recruitment may have appealed to younger, more educated and wealthy pwMS which therefore limits the generalisability of our findings. All correlations that were significant were also weak in nature and therefore despite the large sample size this needs to be considered. In order to clarify the issue of causation, planned longitudinal studies of this sample would need to be carried out. The control paper did report data from an earlier time period, however it used the same food questionnaire and it covered 25,000 people. Some changes would have occurred due to food composition changes and others due to health messages, for example a decrease in fat and sodium and an increase in fruit and vegetables, however these changes would not be large enough to cause worry in the results [37]. Also, employment and race were not reported in the control paper, and therefore this information could not be compared across the cohorts.

In conclusion, this study supports an association between consuming the recommended intakes of a combination of foods and nutrients with pro/ anti-inflammatory properties, and fatigue and HRQOL. Correlations between specific pro/anti-inflammatory dietary factors and particular MS health outcomes warrants further research into dietary modification for pwMS and its potential beneficial effect on MS health outcomes. Further research including randomised controlled trials of nutritional interventions aimed at controlling inflammation is required.

Acknowledgment

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Supplemental materials

Supplemental materials were provided and include: Methods and Table S1, Supplement use amongst 2410 PwMS per day.

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Table 1. Participant Demographics

Variable	N
Gender (%)	
Female	71.4%
n/a	0.1%
Age (years), (mean ± SD)	53 (11.42)
Ethnicity (%)	
White	92.6
Other	3.1
No Answer	0.4
Missing	3.9
Smoke (%)	
Yes	41.7
Missing	16.1
Employment Status (%)	
Working	38.6
Other	53.4
Missing	3.5
Walking Related Symptoms (%)	
Yes	60.9
Missing	2.9
Type of MS (%)	
Relapsing-Remitting	50
Primary Progressive	16
Secondary Progressive	22.8
Missing	2.7

Values are reported in percentages of the total. SD, standard deviation.

Table 2. Nutrient intake in people with Multiple Sclerosis (PwMS) compared to a sample from the general population.

Nutrient	Energy (kcal)	Protein (g)	Alcohol (g)	Carb (g)	Fibre (g)	Fat (g)	Sat fat (g)	Polyunsat fat (g)	Monounsat fat (g)	Calcium (mg)	Iron (mg)	Potassium (mg)	Carotene (microg)	Folate (microg)	Vitamin C (mg)	Vitamin D (microg)	Vitamin E (mg)
PwMS																	
Female	1859	79.80	2	237	18.20	67	25	12.20	22.50	971	11.50	3781	3477	322	123	3.01	12.40
Male	2126	83.40	6.70	261	17.50	78.90	30.10	13.50	27	1021	12.10	3814	3188	320	103	3.16	13.20
Mulligan *et al.* 2014																	
Female	1925	81.5	5.6	247	19	70.8	27	13.5	24.1	992	11.8	3861	3719	332	133	3.46	13.8
Male	2190	85.2	12.3	271	18.2	83.2	32.3	15	28.8	1039	12.4	3881	3321	331	111	3.65	14.9

Intake in PwMS refers to mean data from the 2410 Food Frequency Questionnaires. Average daily nutrient intakes for men (N=11250) and women (N=13602) participating in the EPIC-Norfolk study, from the FETA programmes, after the exclusion of outliers. PwMS: people with Multiple Sclerosis; Carb: carbohydrate; Sat Fat: saturated fat; polyunsat: polyunsaturated; monounsat: monounsaturated.

Table 3. Association between recommended intakes of anti-inflammatory dietary factors and clinical fatigue.

Dietary factors	**Clinical Fatigue [a]**	
Anti-inflammatory dietary factors	r	p
Carotene - total (carotene equivalents),>2000 mcg/d	-0.02	0.42
Magnesium, >270 mg/d	-0.03	0.20
Fish and fish products, >40 g/d	**-0.05**	**0.04***
Oily fish, >1 p/w	-0.05	0.06
Fruit and vegetables, >400 g/d	-0.03	0.18
Fibre, >30 g/d	0.02	0.41
Pro-inflammatory dietary factors		
Sodium, >1600 mg/d	0.01	0.77
Sucrose, >30 g/d	0.03	0.16
Red meat, g/day c, >70 g/d	0.05	0.07
Saturated fat, >30 g/d (men)	0.05	0.25
Saturated fat, >20 g/day (women)	0.03	0.32

[a] Clinical fatigue was defined as an average score (out of all 9 questions) of ≥ 4 out of 7 using the fatigue severity scale. *$p < 0.05$

Table 4. Correlation between recommended intakes of anti-inflammatory and pro-inflammatory dietary factors with total EQ-5D [a] and EQ-5D domains.

	EQ-5D		**Mobility**		**Self-care**		**Usual activities**		**Pain**		**Anxiety/depression**		**Health state** [b]	
Anti-inflammatory dietary factors	r	p	r	p	r	p	r	p	r	p	r	p	r	p
Carotene - total (carotene equivalents),>2000 mcg/d	-0.02	0.28	-0.03	0.16	-0.005	0.792	-0.027	0.184	-0.007	0.726	-0.035	0.086	**0.071**	**0.001**
Magnesium, >270 mg/d	-0.02	0.26	-0.04	0.08	-0.026	0.211	**-0.046**	**0.021**	0.004	0.860	0.002	0.933	**0.045**	**0.030**
Fish and fish products, >40 g/d	-0.02	0.33	-0.02	0.29	0.003	0.882	-0.007	0.730	0.007	0.715	-0.022	0.271	0.008	0.696
Oily fish, >1 p/w	**-0.06**	**<0.01**	**-0.05**	**0.02**	-0.032	0.113	-0.033	-0.096	-0.036	0.071	**-.056**	**0.006**	0.031	0.138
Fruit and vegetables, >400 g/d	-0.03	0.08	-0.02	0.28	**-0.043**	**0.035**	-0.023	0.249	0.009	0.661	**-0.047**	**0.022**	**0.071**	**0.001**
Fibre, >30 g/d	0.04	0.06	-0.01	0.85	**0.051**	**0.013**	**0.060**	**0.003**	**0.048**	**0.018**	0	0.999	**0.041**	**0.046**
Pro-inflammatory dietary factors														
Sodium, >1600 mg/d	-0.02	0.34	0.019	0.360	-0.011	0.578	**-0.043**	**0.035**	0.005	0.802	-0.015	0.474	0.019	0.359
Sucrose, >30 g/d	0.01	0.95	0.003	0.872	-0.018	0.385	-0.020	0.318	0.016	0.433	0.015	0.453	0.007	0.735
Red meat [c], g/day c, >70 g/d	0.03	0.11	0.020	0.346	0.017	0.404	0.039	0.053	**0.040**	**0.048**	**0.058**	**0.004**	-0.032	0.118
Saturated fat, >30 g/d (men)	-0.01	0.77	-0.009	0.822	-0.030	-.427	-0.044	0.245	0.006	0.871	0.001	0.988	0.02	0.598

Saturated fat, >20 g/day (women)	0.03	0.15	0.004	0.860	0.011	0.657	0.029	0.226	0.036	0.135	**0.053**	**0.027**	-0.002	0.930

[a] Includes participants who provided answers for all 5 EQ-5D questions. Total positive EQ-5D ranged from 0-5 where 0=no moderate or severe problems in the health areas covered by the EQ-5D questionnaire, 5= has moderate or severe problems in all areas covered by the EQ-5D questionnaire. 1 point scored for every positive response to each domain. [b] Health state ranged from 0-100 where 0=lowest possible health state, 100=highest possible health state. [c] Includes beef, burgers, pork, lamb, bacon, ham, corned beef, and sausages. [d] Includes single/soured cream, double/clotted cream, full fat/Greek yogurt, dairy desserts, cheese and full cream milk.
* p < 0.05

Table 5. Correlation between recommended intakes of anti-inflammatory and pro-inflammatory dietary factors with total EQ-5D [a] and EQ-5D domains.

	EQ-5D		**Mobility**		**Self-care**		**Usual activities**		**Pain**		**Anxiety/depression**		**Health state** [b]	
Anti-inflammatory dietary factors	r	p	r	p	r	p	r	p	r	p	r	p	r	p
Carotene - total (carotene equivalents),>2000 mcg/d	-0.02	0.28	-0.03	0.16	-0.005	0.792	-0.027	0.184	-0.007	0.726	-0.035	0.086	**0.071**	**0.001**
Magnesium, >270 mg/d	-0.02	0.26	-0.04	0.08	-0.026	0.211	**-0.046**	**0.021**	0.004	0.860	0.002	0.933	**0.045**	**0.030**
Fish and fish products, >40 g/d	-0.02	0.33	-0.02	0.29	0.003	0.882	-0.007	0.730	0.007	0.715	-0.022	0.271	0.008	0.696
Oily fish, >1 p/w	**-0.06**	**<0.01**	**-0.05**	**0.02**	-0.032	0.113	-0.033	-0.096	-0.036	0.071	**-.056**	**0.006**	0.031	0.138
Fruit and vegetables, >400 g/d	-0.03	0.08	-0.02	0.28	**-0.043**	**0.035**	-0.023	0.249	0.009	0.661	**-0.047**	**0.022**	**0.071**	**0.001**
Fibre, >30 g/d	0.04	0.06	-0.01	0.85	**0.051**	**0.013**	**0.060**	**0.003**	**0.048**	**0.018**	0	0.999	**0.041**	**0.046**
Pro-inflammatory dietary factors														
Sodium, >1600 mg/d	-0.02	0.34	0.019	0.360	-0.011	0.578	**-0.043**	**0.035**	0.005	0.802	-0.015	0.474	0.019	0.359
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Red meat [c], g/day c, >70 g/d	0.03	0.11	0.020	0.346	0.017	0.404	0.039	0.053	**0.040**	**0.048**	**0.058**	**0.004**	-0.032	0.118
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Saturated fat, >20 g/day (women)	0.03	0.15	0.004	0.860	0.011	0.657	0.029	0.226	0.036	0.135	**0.053**	**0.027**	-0.002	0.930

[a] Includes participants who provided answers for all 5 EQ-5D questions. Total positive EQ-5D ranged from 0-5 where 0=no moderate or severe problems in the health areas covered by the EQ-5D questionnaire, 5= has moderate or severe problems in all areas covered by the EQ-5D questionnaire. 1 point scored for every positive response to each domain. [b] Health state ranged from 0-100 where 0=lowest possible health state, 100=highest possible health state. [c] Includes beef, burgers, pork, lamb, bacon, ham, corned beef, and sausages. [d] Includes single/soured cream, double/clotted cream, full fat/Greek yogurt, dairy desserts, cheese and full cream milk.

* $p < 0.05$

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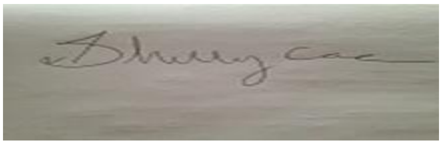

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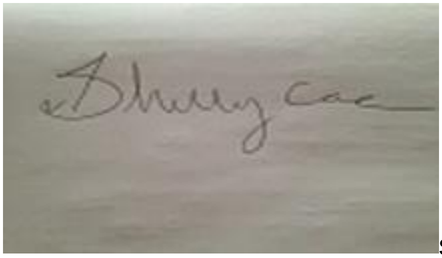

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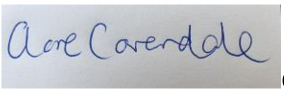
Coverdale C 

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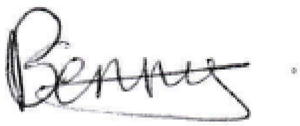

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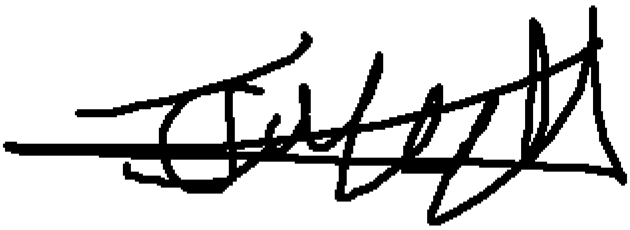

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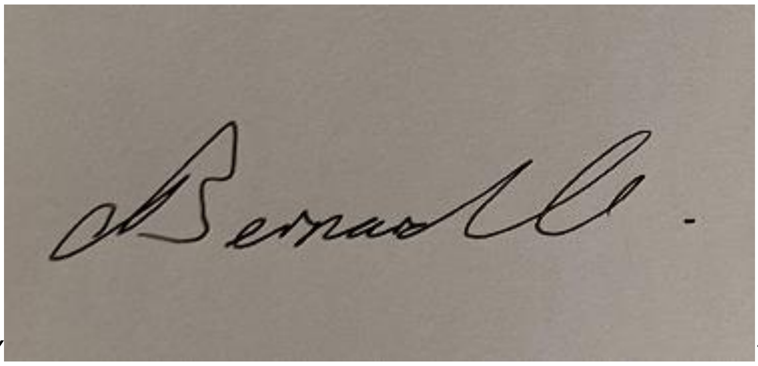
Chu BTY  tszyeungchu@gmail.com
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