Long-term dietary acid load is associated with depression in multiple sclerosis, but less evidence was found with fatigue and anxiety

Long-term dietary acid load is associated with depression in multiple sclerosis, but less evidence for fatigue and anxiety.

Saul, Alice[1], Taylor, Bruce V[1], Blizzard, Leigh[1], Simpson-Yap, Steve[1,2], Probst, Yasmine C[3,4], Black, Lucinda J[5], Ponsonby, Anne Louise[6,7], Broadley, Simon A[8], Lechner-Scott, Jeanette[9,10], Ausimmune/AusLong Investigators Group, van der Mei, Ingrid[1]

1. Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia.

2. Melbourne School of Population & Global Health, The University of Melbourne, Melbourne, Australia.

3. Illawarra Health and Medical Research Institute, Wollongong, Australia.

4. School of Medicine, University of Wollongong, Wollongong, Australia.

5. Curtin School of Population Health, Curtin University, Perth, Australia

6. Murdoch Children's Research Institute, Royal Children's Hospital, University of Melbourne, VIC, Australia

7. The Florey Institute of Neuroscience & Mental Health, Parkville, VIC, Australia

8. School of Medicine, Griffith University, Gold Coast, Australia

9. Department of Neurology, John Hunter Hospital, Newcastle, New South Wales, Australia

10. Faculty of Medicine and Public Health, Hunter Medical Research Institute, University of Newcastle, Newcastle, New South Wales, Australia

Characters title (no spaces): 110 Number of words in abstract: 250 Number of words body manuscript: 3267 Number of figures: 0 Number tables: 4 Number references:45

Please address all correspondence to: I van der Mei, Menzies Institute for Medical Research, Private Bag 23, Hobart, Tasmania, Australia 7001; Email: Ingrid.vanderMei@utas.edu.au; Tel +61 3 6226 7700, Fax +61 3 62267704

Keywords: Diet, potential renal acid load score and net endogenous acid production (NEAP), Multiple Sclerosis, depression, anxiety, fatigue.

Abstract

Background: Diet-dependent acid-base load has been associated with worsening in mental health, but to date no study has examined this in people with multiple sclerosis (PwMS). We examined the association between potential renal acid load (PRAL) and net endogenous acid production (NEAP) scores and depression, anxiety, and fatigue in PwMS.

Methods: Participants with a first clinical diagnosis of CNS demyelination were followed prospectively as part of the AusLong Study (aged 18-59 years at cohort entry). At baseline, 5- and 10-year reviews, PRAL and NEAP scores were calculated using dietary intake in the preceding 12 months calculated from a food frequency questionnaire. At 5- and 10-year reviews, the Hospital Anxiety and Depression Scale was used to assess depression and anxiety, and the Fatigue Severity Scale assessed fatigue.

Results: Higher PRAL and NEAP scores were associated with increased subsequent absolute value and change in HADS depression scores over five years' follow-up (e.g., highest vs lowest PRAL quartile, 5-year change in HADS-D score: β=+3.01, 95%CI= 1.54, 4.48, p<0.001). The level of depression at the 10-year review was determined by both the baseline dietary acid scores and baseline-5-year changes in dietary acid scores (e.g., PRAL change from baseline to 5-year review, 10-year review HADS-D score:β=+0.09, 95%CI= 0.03, 0.15, p<0.001). Some associations were observed with anxiety and fatigue, but were weaker and less consistent.

Conclusion: Our findings indicate that a higher dietary acid load potentially has a long-term influence on the level of depression in PwMS. The evidence is less convincing for anxiety and fatigue.

Introduction

Multiple sclerosis (MS) is an autoimmune neurodegenerative disease of the central nervous system. The prevalence of depression (19% [1]), anxiety (45% [1]), and fatigue (53-90%[2]) in MS is higher than that seen in people who are not diagnosed with MS (depression 8%, anxiety 11%) [3]. In addition, fatigue in MS is neuropathic and not merely secondary to exertion as is common to some chronic conditions, and therefore not relieved by rest [4]. All three (depression, anxiety, and fatigue) severely impact the quality of life of people living with MS [5].

While many people with MS modify their eating habits, at present, there is insufficient evidence to support specific dietary interventions that benefit those with MS. Trials often have issues with the design or implementation or are too heterogeneous to compare [6]. The use of composite diet scores, such as a dietary acid load, is an alternative method of examining diet data in MS.

Diet scoring indices have been created to measure dietary acid loads, for example the potential renal acid load (PRAL), the net endogenous acid production (NEAP) and a ratio of animal protein to potassium (A:P) [7, 8]. PRAL is a measure of dietary induced acidity (foods that release acid precursors post metabolism) or alkalinity (foods that release precursors of bases) of the bloodstream. It is based on five nutrients (protein, phosphorus, potassium, magnesium, and calcium) [9]. NEAP uses two nutrients, protein and potassium, which has also been shown to be representative of dietary induced acidity/alkalinity [9].

There is evidence that a higher dietary acid load is associated with the risk of depression and anxiety in the general population (children, adolescents, and adults [10-12]), as well as in females with diabetes [13] and breast cancer survivors [14]. For example, a study (n=4,378) in healthy Iranian adults found that a higher dietary acid load, as measured by the A:P ratio, was

associated with an increased risk of depression (highest vs lowest quartile: $OR_{A:}$=1.57; 95%CI=1.27-1.95, P_{trend}<0.001 and anxiety (highest vs lowest quartile: $OR_{A:P}$=1.92; 95% CI=1.35-2.74, P_{trend}<0.001) [11]. Another Iranian study in healthy adult women (n=477) found that higher PRAL and NEAP were associated with increased depression (highest vs lowest tertile: OR_{PRAL}: 3.63; 95% CI:1.97, 6.71; P_{trend}=0.0001, OR_{NEAP}:3.42; 95 %CI: 1.87, 6.23; P_{trend}=0.0001) and anxiety (highest vs lowest tertile: OR_{PRAL}: 3.31; 95 %CI: 1.81, 6.06; P_{trend}=0.0001, OR_{NEAP}:3.47; 95 %CI: 1.90, 6.33; P_{trend}=0.0001) [12]. Both cross-sectional studies could not assess the associations prospectively and thus the findings could be due to reverse causality. A prospective study, however, conducted in children and adolescents, found that children with a higher PRAL at baseline had a worsening mental health after 10 years with subsequently more emotional problems (OR=1.33 (95%CI=1.15-1.54); p<0.001) and hyperactivity (1.22 (1.04- 1.43); p=0.014), while no associations were found with mental health after 15 years [10].

While there is evidence for dietary acid load having an impact on mental health in the general population and some disease populations, there are no studies in people with MS that have examined associations between dietary acid load and depression, anxiety, and fatigue. We, therefore, examined these relationships in a cohort of people with a first clinical diagnosis of central nervous system (CNS) demyelination followed annually over 10 years, with the hypothesis that higher dietary acid load scores (more acidic diet) are associated with higher levels of depression, anxiety, and fatigue.

Methods

Ausimmune Longitudinal (AusLong) Study

Cases with a first clinical diagnosis of CNS demyelination (optic neuritis, transverse myelitis, brainstem syndrome or other) were recruited into the Ausimmune Study (a multicentre, case-control study) and then followed prospectively in the AusLong Study (aged 18-59 years at cohort entry). The Ausimmune Study recruited 282 participants. At follow-up, three participants were excluded because their initial event was due to a non MS condition. Of the 279 participants, 236 participated at the 5-year review and 225 at the 10-year review. We included only those who had converted to MS (2005 McDonald criteria) [15] by the 10-year review (n=190). Of those, data was available for n=179 (94.2%) on anxiety and depression, n=180 for fatigue (94.7%), and n=184 for dietary measures (96.8%).

Ethical approval of the study was provided by the human research committees associated with each of the participating centres in Tasmania, (Human Research Ethics Committee Tasmania Network, ethics number: H0010499), Queensland (Royal Brisbane and Women's Hospital Ethics Committee, ethics number: HREC/09/QRBW/299 and the Griffith University Human Research Ethics Committee, ethics number: MED/02/10/HREC), New South Wales (Hunter New England Local Health District, ethics number: 09/04/15/5.04) and Victoria (Barwon Health, ethics number: 09/24). All participants provided written informed consent.

Dietary acid load

A validated [16] semi-quantitative food frequency questionnaire, the Dietary Questionnaire for Epidemiological Studies (DQES v2)[17], was used to assess habitual dietary intake over the previous 12 months. The questionnaire was administered at baseline, 5- and 10-year reviews.

To assess dietary acid load, we derived two indices from the dietary intake data, the PRAL and the NEAP. Both measures have been validated and have been shown to reflect a long-term diet acid intake [18-20]. Higher values of the PRAL and NEAP reflect more acidic

dietary intake, whereas lower values indicate more alkaline dietary intake. The PRAL score considers the average intestinal absorption rates for dietary proteins and minerals, ionic dissociation, and sulphur metabolism, while the NEAP just considers protein and potassium. The PRAL was calculated using the formula: PRAL (milliequivalent (mEq)/day) = (0.4888 × total protein[g/day]) + (0.0366 × phosphorus[mg/day]) − (0.0205 × potassium[mg/day]) − (0.0263 × magnesium[mg/day]) − (0.0125 × calcium[mg/day]).

The NEAP was calculated using the formula: NEAP (mEq/day) = (54.5 × protein[g/day]) / (0.0366 × potassium[mEq/day]) – 1.02 [21, 22].

To account for the participants reporting accuracy of their dietary intake, we estimated dietary reporting based on the ratio of total energy intake (EI) to basal metabolic rate (BMR) ratio (EI/BMR). BMR was calculated based on weight and age using the Harris and Benedict [23] equations. Under-reporters were defined by Goldberg cut-off points using an EI/BMR ratio less than 0.87; reliable reporters between 0.87-2.75, and over-reporters above 2.75[24]. Those with implausible energy intakes (>20,000 and <3,000 kJ/day) were excluded (n=2 at the 5-year review and n=11 at the 10-year review).

Outcome measures

Depression and Anxiety

At the 5- and 10-year reviews, depressive and anxiety were assessed using the Hospital Anxiety and Depression Scale (HADS-D and HADS-A, respectively), each comprising 7 items scored 0-3 and summed to establish total scores 0-21 [25]. The HADS has been validated in people with MS [25].

Fatigue

Fatigue was assessed at the 5- and 10-year reviews using the Fatigue Severity Scale (FSS), which was developed and validated for use in MS populations [26]. The FSS comprises of nine Likert scale items, each scored 1-7 and the total score the average of these. Before answering the FSS, participants were asked if they experienced any symptoms of fatigue (yes/no). If no, they were given an FSS score of 0 (no fatigue).

Other factors

Face-to-face interviews with the study nurse at baseline, 5- and 10-year reviews recorded participant demographic and clinical measurements, with height and weight used to calculate body mass index (BMI, weight in kg/height in m^2). Neurological reviews were also performed at these time points by a study neurologist, including disability (Expanded Disability Status Scale (EDSS)), [27] and relapses since previous face-to-face review. The latter were validated by medical records.

Annual telephone reviews focused on changes in factors since the previous review including: use of antidepressant and anxiolytic/sedative medications, medications used to treat fatigue, whether employed (yes/no), whether they changed their diet or supplement use since last review (yes/no), total number of days in the past 12 months doing any vigorous physical activity of >10 minutes (modified version of International Physical Activity Questionnaire)[28], median weekly income ($AUD), education status, smoking status, and presence and severity of 16 stressful life events (modified version of Social Readjustment Rating Scale,[29] scored as total number of events, number of positive events, and number of negative events).

Statistical analysis

To examine the association of dietary acid load in the previous 12 months, we examined whether dietary acid load at 5- and 10-year reviews was associated with HADS and FSS

outcomes at the 5- and 10-year reviews. To assess the longer-term prospective effects, we examined whether dietary acid load at baseline and 5-year review were associated with anxiety depression and fatigue measures five years later (5- and 10-year review, respectively). Both analyses used transformed linear mixed-effects models for repeated measures, transformation thetas derived by Box-Cox regression and clustering on the participant. However, all results were then back transformed and presented on the original scale of the outcome variable at the means of model covariates.

We also used linear regression to examine whether dietary acid load at the 5-year review was associated with a subsequent change in outcomes (5-year to 10-year review).

To estimate the relative contributions of the current and past dietary measures on the outcomes (depression/anxiety/fatigue) at 10-year review, the outcome values were regressed on covariates for the current and all past values of the dietary measures. This approach allowed us to make use of the baseline dietary measures. The estimated coefficients are reported as numerically equivalent sums of coefficients or differences between coefficients to aid interpretation of the results [30, 31].

We examined confounding using standard definitions of confounding [32] [33], [34]. We adjusted for age, sex, total energy intake, and dietary reporting as a dichotomous term (under-reporters/over-reporters versus reliable reporters) in all models to limit measurement bias. We adjusted for BMI within the PRAL analyses as it satisfied all the rules of confounding.

We performed sensitivity analyses to determine whether there was an underlying effect of chronic metabolic acidosis or alkalosis by excluding those with a history of diabetes (n=7). A Spearman's correlation coefficient was used to test the correlation between PRAL and NEAP.

All analyses were completed using STATA/SE 16.1 (StataCorp LP, College Station, USA).

Results

Table 1 shows the demographic details of the assessed cohort. The PRAL ranged from -14.30 to 85.00 (mean: 20.09, SD: 14.92) and the NEAP ranged from 34.75 to 107.00 (mean: 66.29, SD: 12.64) (Table 1). The correlation between PRAL and NEAP was 0.81.

Associations with depression

Dietary acid load in the previous 12 months was not associated with the level of depression (Table 2).

When assessing the prospective effects, we observed a significant association between a higher PRAL and NEAP score and a higher HADS-D score five years later when the PRAL and NEAP scores were examined in the continuous form, but when assessed as categorical variables it became clear that this was largely driven by the top quartiles of each (Table 2).

Clearer associations were demonstrated when examining change in levels of depression from 5 to 10 years, with a clear dose-response present and a significant test for trend (Table 3). For example, those in the lowest PRAL quartile (PRAL between -41.85 to 10.80; the reference category) had a mean decrease in HADS-D of -1.60, whilst those in the highest PRAL quartile (PRAL of >26.24) had a mean relative change in the HADS-D of +3.01 compared to those in the adjusted, lowest quartile, and thus an absolute change +1.41 (-1.60 + 3.01), which means their level of depression worsened by 1.41 HADS D points compared to a 1.6 point improvement for those in the lowest quartile.

We examined the patterns of association between the dietary acid variables and level of depression at the10-year review. We found that a higher baseline PRAL and NEAP score was associated with higher levels of depression at the10-year review, with independent

associations observed for increases in PRAL and NEAP from baseline to 5-year review and from 5-year to 10-year review (Table 4).

Associations with anxiety

No associations were seen between PRAL or NEAP scores and anxiety, either when examined in the previous 12 months or prospectively, including both absolute anxiety and change in anxiety over five years (Table 2-3).

When examining the patterns of association with the level of anxiety at 10-year review, we found that higher baseline PRAL and NEAP score was associated with higher levels of anxiety at the 10-year review, with independent associations similarly observed for increases in PRAL and NEAP from baseline to 5-year review and from 5- to 10-year review (Table 4).

Associations with fatigue

Dietary acid load in the previous 12 months was not associated with levels of fatigue (p>0.09, Table 2).

When assessing prospective associations, there was little evidence that PRAL or NEAP at baseline and 5-year review was associated with higher levels of fatigue five years later (Table 2). However, there were dose-dependent associations between PRAL at the 5-year review and change in levels of fatigue from 5 to 10 years, with a significant test for trend and the highest quartile significantly associated (Table 3). Those in the lowest PRAL quartile (PRAL between -41.85 to 10.80) had a mean increase in FSS of +0.31, while those in the highest PRAL quartile (PRAL of >26.24) had a mean relative change in the FSS of +1.16 compared to those in the adjusted lowest quartile, and thus an absolute change +1.47 (0.31 + 1.16),

which means their FSS score worsened by 1.47 units. There was a significant association between NEAP at the 5-year review and change in levels of fatigue from 5 to 10-years in the continuous form, FSS increasing by 0.03 (p=0.03); however, no significant associations were found when examining the categorical form.

We did not find any associations between baseline dietary acid load scores or changes in dietary acid load (PRAL or NEAP) with fatigue at the 10-year review (Table 4).

Sensitivity analysis

To assess the possibility that a worsening in kidney function, which plays a major role in acid-base balance, could have influenced our main findings, we limited to those without a history of diabetes and found no change (data not shown).

Discussion

In a prospective cohort of people with MS, we found that a higher dietary acid load was associated with an increase in absolute value and change in depression levels over five years, and that the level of depression at the 10-year review was determined by both the baseline dietary acid scores as well as the changes in acid scores from baseline to 5-year and from 5- to 10-year reviews. Some associations in the same direction were observed with anxiety and fatigue but were less consistent.

When we assessed dietary acid load and subsequent 5-year change in depression, we found a strong, positive association, such that those in the lowest, more alkaline PRAL quartile had a mean absolute change in HADS-D of -1.60 points (reduction in depression), and those in the highest, more acidic PRAL quartile had a mean relative change in HADS-D of +3.01 when compared to those in the reference category. This is clinically meaningful when compared to a previously described clinically meaningful difference of 1.7 points in HADS -D [35]. We also found that a higher dietary acid load was associated with higher subsequent levels of depression. When examining the level of depression at the 10-year review, we observed independent associations for higher dietary acid load scores at baseline as well as a further worsening in dietary acid load from baseline to 5-year and from 5- to 10-year, suggesting that both baseline dietary acid load and change in dietary acid load are determining long-term depression levels. The finding that our associations were stronger when depression was assessed five years after the dietary acid load compared to when we examined acid load and depression at the same time suggests that the effects of acid load occur over a longer timeframe. If these associations are indeed causal, then interventions that reduce the dietary acid load longer term may be effective in lowering depression levels in people with MS.

For anxiety, we found no associations between dietary acid load and anxiety, neither when examined in the previous 12 months nor prospectively, including both absolute anxiety and change in anxiety over five years. However, when examining 10-year anxiety as an outcome and modelling both baseline dietary acid load and change in dietary acid load, we found that baseline dietary acid load as well as changes in dietary acid load were associated with 10-year anxiety with effect sizes that were of a similar magnitude as seen for depression. It is unclear why there is little alignment between the different types of analyses.

No other studies have examined these associations with depression or anxiety in MS; however, two large cross-sectional studies in the general population (Iranian adults) found that higher dietary acid loads were associated with a higher risk of depression and anxiety [11, 12]. While those cross-sectional studies could not assess associations prospectively or assess reverse causality, they also differ from our study in using a calculation for dietary acid load that has fewer nutrients [11] and different assessment of depression and anxiety [11, 12].

In terms of the biological mechanisms that may underlie the observed associations, a dietary intake rich in acidic foods (e.g. meat, fish, grains and cheese) and low in alkaline foods (e.g. fruits, vegetables, milk, yogurt (less acid source of animal protein, textured soy protein) [36] can increase the activity of glucocorticoids [37]. A recent study in mice showed that changes in the gut microbiome led to an increased display of anxiety and depression symptoms through the downstream pathway of the glucocorticoid receptor [38]. Dietary induced acid load has also been positively associated with the future development of insulin resistance, [39, 40] Insulin resistance is more prevalent among people with MS [41], has been associated with a worsening in mental health in the general population [42] and can be induced in mice by an excess of glucocorticoids [43]. Another potential mechanism is that dietary proteins interact with certain genetic polymorphisms. For example, an interaction was found in those who had a dietary intake that was high in meat and low in fat intake (high dietary acid load),

and variation in the rs7041 polymorphism of the vitamin D-binding protein (VDBP) gene ($p_{interaction=}$ 0.03). Carriers of the T allele who had a more acidic diet had a higher prevalence of depression [44].

To our knowledge there are no studies in people with MS that have examined the association between dietary acid load and fatigue. We found some evidence that longer-term dietary acid load may be associated with a change in fatigue; however, effect sizes were modest, and they appeared to be driven by the highest category only. There were no associations with actual fatigue level, either when dietary acid loads were examined at the same time as the fatigue level or when assessed prospectively. There also were no association when examining baseline dietary acid load and changes in dietary acid load with the level of fatigue at the 10-year review. Taken together, this does not provide convincing evidence that the dietary acid load scores are meaningfully associated with fatigue in people with MS.

A strength of our study was the ability to assess a large variety of environmental factors as potential confounders in this longitudinal study, allowing a robust assessment of the independence of our associations. Further, this is a prospective study, allowing us to examine associations with the correct temporality, and allowing us to examine different types of models. However, we cannot totally rule out reverse causality. We used two measures of dietary acid load, and we found that our findings were generally consistent, irrespective of which acid load measure was used. While we do not have any measures of kidney function, and participants could have used medications or supplements which may have played a role in acid-base balance, we performed sensitivity analyses to determine whether there was an underlying effect of chronic metabolic acidosis or alkalosis by excluding those with a history of diabetes and found our results did not change, giving confidence to our findings.

In conclusion, we found evidence that a higher dietary acid load may have a long-term effect on increasing absolute level and change in depression scores. The evidence was less convincing for anxiety and fatigue but in the same direction. If the associations observed with depression are replicated and causal, then the longer-term consumption of more alkaline diets or avoidance of acidic diets could be a potential point of intervention to improve depression in people with MS.

Acknowledgements

We express our heartfelt thanks to the participants in the Ausimmune and AusLong studies for their time and energy, without which we could not have undertaken this work.

The authors also thank the research personnel, including the local research officers: Susan Agland, Hunter New England Health, Newcastle, New South Wales; Barbara Alexander , Queensland Institute for Medical Research, Queensland; Marcia Davis, Queensland Institute for Medical Research, Queensland; Zoe Dunlop, Barwon Health, Geelong Hospital, Victoria; Rosalie Scott, Royal Brisbane and Women's Hospital, Queensland; Marie Steele, Royal Brisbane and Women's Hospital, Queensland; Catherine Turner, Menzies Research Institute, Tasmania; Brenda Wood, Menzies Research Institute, Tasmania; and the Ausimmune Study project officers during the course of the study: Jane Gresham, National Centre for Epidemiology and Population Health, The Australian National University, Canberra; Australian Capital Territory; Camilla Jozwick, National Centre for Epidemiology and Population Health, The Australian National University, Canberra; Australian Capital Territory; Helen Rodgers, National Centre for Epidemiology and Population Health, The Australian National University, Canberra; Australian Capital Territory.

The members of the Ausimmune/AusLong Investigators Group are as follows: Robyn M Lucas (National Centre for Epidemiology and Population Health, Canberra), Keith Dear (University of Adelaide, Australia), Anne-Louise Ponsonby and Terry Dwyer (Murdoch Childrens Research Institute, Melbourne, Australia), Ingrid van der Mei, Leigh Blizzard, Steve Simpson-Yap, and Bruce V Taylor (Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia), Simon Broadley (School of Medicine, Griffith University, Gold Coast Campus, Australia), Trevor Kilpatrick (Centre for Neurosciences, Department of Anatomy and Neuroscience, University of Melbourne, Melbourne, Australia). David Williams and Jeanette Lechner-Scott (University of Newcastle, Newcastle, Australia), Cameron Shaw and Caron Chapman (Barwon Health, Geelong, Australia), Alan Coulthard (University of Queensland, Brisbane, Australia), Michael P Pender (The University of Queensland, Brisbane, Australia) and Patricia Valery (QIMR Berghofer Medical Research Institute, Brisbane, Australia).

Conflicts of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

[1] Wood B et al (2013) Prevalence and concurrence of anxiety, depression and fatigue over time in multiple sclerosis. Mult Scler 19: 217-24. https://doi.org/10.1177/1352458512450351

[2] Strober LB (2015) Fatigue in multiple sclerosis: a look at the role of poor sleep. Front Neurol 6: 21. https://doi.org/10.3389/fneur.2015.00021

[3] Simpson S, Jr., Pittas F, van der Mei I, Blizzard L, Ponsonby AL, and Taylor B (2011) Trends in the epidemiology of multiple sclerosis in Greater Hobart, Tasmania: 1951 to 2009. J Neurol Neurosurg Psychiatry 82: 180-7. https://doi.org/10.1136/jnnp.2010.215186

[4] Chalah MA, Riachi N, Ahdab R, Creange A, Lefaucheur JP, and Ayache SS (2015) Fatigue in Multiple Sclerosis: Neural Correlates and the Role of Non-Invasive Brain Stimulation. Front Cell Neurosci 9: 460. https://doi.org/10.3389/fncel.2015.00460

[5] Simpson S, Jr. et al (2016) Anxiety, depression and fatigue at 5-year review following CNS demyelination. Acta Neurol Scand 134: 403-413. https://doi.org/10.1111/ane.12554

[6] Parks NE, Jackson-Tarlton CS, Vacchi L, Merdad R, and Johnston BC (2020) Dietary interventions for multiple sclerosis-related outcomes. Cochrane Database Syst Rev 5: CD004192. https://doi.org/10.1002/14651858.CD004192.pub4

[7] Frassetto LA, Todd KM, Morris RC, Jr., and Sebastian A (1998) Estimation of net endogenous noncarbonic acid production in humans from diet potassium and protein contents. Am J Clin Nutr 68: 576-83. https://doi.org/10.1093/ajcn/68.3.576
[8] Zwart SR, Hargens AR, and Smith SM (2004) The ratio of animal protein intake to potassium intake is a predictor of bone resorption in space flight analogues and in ambulatory subjects. Am J Clin Nutr 80: 1058-65. https://doi.org/10.1093/ajcn/80.4.1058
[9] Kahleova H et al (2021) A plant-based diet in overweight adults in a 16-week randomized clinical trial: The role of dietary acid load. Clin Nutr ESPEN 44: 150-158. https://doi.org/10.1016/j.clnesp.2021.05.015
[10] Buhlmeier J et al (2018) Dietary Acid Load and Mental Health Outcomes in Children and Adolescents: Results from the GINIplus and LISA Birth Cohort Studies. Nutrients 10. https://doi.org/10.3390/nu10050582
[11] Milajerdi A, Hassanzadeh Keshteli A, Haghighatdoost F, Azadbakht L, Esmaillzadeh A, and Adibi P (2020) Dietary acid load in relation to depression and anxiety in adults. J Hum Nutr Diet 33: 48-55. https://doi.org/10.1111/jhn.12658
[12] Mozaffari H, Siassi F, Guilani B, Askari M, and Azadbakht L (2020) Association of dietary acid-base load and psychological disorders among Iranian women: A cross-sectional study. Complement Ther Med 53: 102503. https://doi.org/10.1016/j.ctim.2020.102503
[13] Daneshzad E, Keshavarz SA, Qorbani M, Larijani B, Bellissimo N, and Azadbakht L (2020) Association of dietary acid load and plant-based diet index with sleep, stress, anxiety and depression in diabetic women. Br J Nutr 123: 901-912. https://doi.org/10.1017/S0007114519003179
[14] Wu T, Hsu FC, and Pierce JP (2020) Acid-Producing Diet and Depressive Symptoms among Breast Cancer Survivors: A Longitudinal Study. Cancers (Basel) 12. https://doi.org/10.3390/cancers12113183
[15] McDonald WI et al (2001) Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol 50: 121-7. https://doi.org/10.1002/ana.1032
[16] Khalesi S, Doshi D, Buys N, and Sun J (2017) Validation of a short food frequency questionnaire in Australian adults. Int J Food Sci Nutr 68: 349-357. https://doi.org/10.1080/09637486.2016.1240763
[17] Ireland P et al (1994) Development of the Melbourne FFQ: a food frequency questionnaire for use in an Australian prospective study involving an ethnically diverse cohort. Asia Pac J Clin Nutr 3: 19-31.
[18] Remer T and Manz F (1995) Potential renal acid load of foods and its influence on urine pH. J Am Diet Assoc 95: 791-7. https://doi.org/10.1016/S0002-8223(95)00219-7
[19] Michaud DS et al (2003) Comparison of estimated renal net acid excretion from dietary intake and body size with urine pH. J Am Diet Assoc 103: 1001-7; discussion 1007. https://doi.org/10.1016/s0002-8223(03)00469-3
[20] Scialla JJ and Anderson CA (2013) Dietary acid load: a novel nutritional target in chronic kidney disease? Adv Chronic Kidney Dis 20: 141-9. https://doi.org/10.1053/j.ackd.2012.11.001
[21] Akter S et al (2017) Dietary acid load and mortality among Japanese men and women: the Japan Public Health Center-based Prospective Study. Am J Clin Nutr 106: 146-154. https://doi.org/10.3945/ajcn.117.152876

[22] Park YM et al (2018) Higher diet-dependent acid load is associated with risk of breast cancer: Findings from the Sister Study. Int J Cancer. https://doi.org/10.1002/ijc.31889
[23] Harris J and Benedict F, *A biometric study of basal metabolism in man*. Wasthington D.C.: Carnegie Institute of Washington, 1919.
[24] Goldberg GR et al (1991) Critical evaluation of energy intake data using fundamental principles of energy physiology: 1. Derivation of cut-off limits to identify under-recording. Eur J Clin Nutr 45: 569-81.
[25] Snaith RP and Zigmond AS (1986) The hospital anxiety and depression scale. Br Med J (Clin Res Ed) 292: 344. https://doi.org/10.1136/bmj.292.6516.344
[26] Krupp LB, LaRocca NG, Muir-Nash J, and Steinberg AD (1989) The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 46: 1121-3.
[27] Kurtzke JF (1983) Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 33: 1444-52.
[28] Craig CL et al (2003) International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 35: 1381-95. https://doi.org/10.1249/01.MSS.0000078924.61453.FB
[29] Holmes TH and Rahe RH (1967) The Social Readjustment Rating Scale. J Psychosom Res 11: 213-8. https://doi.org/10.1016/0022-3999(67)90010-4
[30] Mishra G, Nitsch D, Black S, De Stavola B, Kuh D, and Hardy R (2009) A structured approach to modelling the effects of binary exposure variables over the life course. Int J Epidemiol 38: 528-37. https://doi.org/10.1093/ije/dyn229
[31] Smith AD et al (2016) A structured approach to hypotheses involving continuous exposures over the life course. Int J Epidemiol 45: 1271-1279. https://doi.org/10.1093/ije/dyw164
[32] Hernan MA, Hernandez-Diaz S, Werler MM, and Mitchell AA (2002) Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. Am J Epidemiol 155: 176-84.
[33] Willett WC, Howe GR, and Kushi LH (1997) Adjustment for total energy intake in epidemiologic studies. Am J Clin Nutr 65: 1220S-1228S; discussion 1229S-1231S. https://doi.org/10.1093/ajcn/65.4.1220S
[34] Anton SD and Miller PM (2005) Do negative emotions predict alcohol consumption, saturated fat intake, and physical activity in older adults? Behavior modification 29: 677-88. https://doi.org/10.1177/0145445503261164
[35] Lemay KR, Tulloch HE, Pipe AL, and Reed JL (2019) Establishing the Minimal Clinically Important Difference for the Hospital Anxiety and Depression Scale in Patients With Cardiovascular Disease. J Cardiopulm Rehabil Prev 39: E6-E11. https://doi.org/10.1097/HCR.0000000000000379
[36] Rodrigues Neto Angeloco L, Arces de Souza GC, Almeida Romao E, and Garcia Chiarello P (2018) Alkaline Diet and Metabolic Acidosis: Practical Approaches to the Nutritional Management of Chronic Kidney Disease. J Ren Nutr 28: 215-220. https://doi.org/10.1053/j.jrn.2017.10.006
[37] Weiner ID (2016) Untangling the complex relationship between dietary acid load and glucocorticoid metabolism. Kidney Int 90: 247-249. https://doi.org/10.1016/j.kint.2016.04.011
[38] Luo Y et al (2018) Gut microbiota regulates mouse behaviors through glucocorticoid receptor pathway genes in the hippocampus. Transl Psychiatry 8: 187. https://doi.org/10.1038/s41398-018-0240-5

[39] DiNicolantonio JJ and O'Keefe JH (2021) Low-grade metabolic acidosis as a driver of insulin resistance. Open Heart 8. https://doi.org/10.1136/openhrt-2021-001788
[40] Akter S et al (2016) High dietary acid load is associated with insulin resistance: The Furukawa Nutrition and Health Study. Clin Nutr 35: 453-459. https://doi.org/10.1016/j.clnu.2015.03.008
[41] Soliman RH, Farhan HM, Hegazy M, Oraby MI, Kamel SH, and Hassan A (2020) Impact of insulin resistance and metabolic syndrome on disability in patients with multiple sclerosis. The Egyptian Journal of Neurology, Psychiatry and Neurosurgery 56: 18. https://doi.org/10.1186/s41983-020-0155-y
[42] Watson KT et al (2021) Association of Insulin Resistance With Depression Severity and Remission Status: Defining a Metabolic Endophenotype of Depression. JAMA Psychiatry 78: 439-441. https://doi.org/10.1001/jamapsychiatry.2020.3669
[43] Beaupere C, Liboz A, Feve B, Blondeau B, and Guillemain G (2021) Molecular Mechanisms of Glucocorticoid-Induced Insulin Resistance. Int J Mol Sci 22. https://doi.org/10.3390/ijms22020623
[44] Pooyan S et al (2018) A High-Protein/Low-Fat Diet May Interact with Vitamin D-Binding Protein Gene Variants to Moderate the Risk of Depression in Apparently Healthy Adults. Lifestyle Genom 11: 64-72. https://doi.org/10.1159/0004924

Table 1. Characteristics of the participants

	5-year review		10-year review	
	n	**Mean (SD; Range)**	**n**	**Mean (SD; Range)**
Age (years)	190	44.5 (9.7; 23.4 – 63.5)	190	48.7 (9.7; 27.9 – 68.2)
PRAL score* (mEq /day)	183	20.1 (14.9; -14.3 – 85.0)	175	19.27 (12.8; -21.7 – 61.4)
NEAP score* (mEq /day)	183	66.3 (12.6; 34.8 – 107.0)	175	65.38 (12.3; 26.6 – 104.1)
Days per week of vigorous physical activity in last 12 months	190	1.8 (2.0; 0.0 – 7.0)	190	1.7 (2.0; 0 – 7)
BMI (kg/m^2)	190	27.4 (5.9; 17.5 – 46.2)	190	27.9 (6.3; 17.5 – 49.7)
Total energy intake (kJ/day), excluding those with implausible intakes	181	7087.9 (2562.5; 3091.9 – 17115.4)	176	6570.8 (2228.6; 3032.3 – 15699.6)
	n	**Median (IQR)**	**n**	**Median (IQR)**
HADS Depression score*	179	4 (6)	188	3 (6)
HADS Anxiety score*	179	7 (5)	188	6 (5.5)
FSS*	190	4.8 (2.7)	189	4.8 (2.8)
	n/N		**n/N**	
Female sex	153/190			
Diabetes (yes/no)			7/190	
Disease modifying therapies (yes/no)	148/190		149/190	

*HADS: Hospitality Anxiety and Depression Scale; FSS: Fatigue Severity Scale; BMI: Body Mass Index; PRAL: Potential Renal Acid Load; NEAP: Net Endogenous Acid Production. FFQ: Food Frequency Questionnaire.

Table 2: The association between absolute values of dietary acid load indices with depression, anxiety, and fatigue.

	Depression				Anxiety		Fatigue			
	N[5]	**N[10]**	**β*(95%CI)**	***p***	**β*(95%CI)**	***p***	**N[5]**	**N[10]**	**β*(95%CI)**	***p***
Dietary acid load in the previous 12 months (5- and 10-year review) and outcomes at the same review (5- and 10-year review).										
PRAL Score Continuous form	175	175	-0.02 (-0.05 to 0.01)	0.24	0.00 (-0.03 to 0.03)	0.92	180	175	-0.02 (-0.05 to 0.00)	0.09
PRAL Score Categorical form										
-41.85 to 10.80	45	42	0.00 (Ref)		0.00 (Ref)				0.00 (Ref)	
10.81 to 17.44	47	49	**-1.10 (-2.07 to -0.13)**	**0.03**	-0.46 (-1.31 to 0.40)	0.29	45	42	-0.20 (-0.97 to 0.58)	0.62
17.45 to 26.24	37	44	-0.71 (-1.79 to 0.38)	0.20	0.41 (-0.56 to 1.37)	0.41	49	48	-0.29 (-1.13 to 0.56)	0.51
>26.24	46	40	-1.11 (-2.39 to 0.18)	0.09	0.31 (-0.90 to 1.51)	0.62	39	44	-0.62 (-1.63 to 0.38)	0.22
Test for trend:				0.13		0.38	47	41		0.24
NEAP Score Continuous form	175	175	-0.01 (-0.04 to 0.02)	0.48	0.02 (-0.01 to 0.04)	0.29	180	175	-0.01 (-0.04 to 0.01)	0.31
NEAP Score Categorical form										
15.15 to 58.35	48	42	0.00 (Ref)		0.00 (Ref)				0.00 (Ref)	
58.36 to 64.82	41	55	-0.54 (-1.46 to 0.37)	0.24	0.27 (-0.58 to 1.12)	0.54	48	41	-0.04 (-0.78 to 0.70)	0.91
64.83 to 73.63	39	41	-0.62 (-1.64 to 0.41)	0.24	0.13 (-0.83 to 1.09)	0.79	43	55	-0.24 (-1.05 to 0.58)	0.57
>73.63	47	37	-0.23 (-1.27 to 0.81)	0.67	0.68 (-0.30 to 1.65)	0.17	42	41	-0.12 (-0.94 to 0.70)	0.77

Test for trend:				0.67		0.22	47	38		0.69
Dietary acid load (Baseline and 5-year review) and outcomes five years later (5- and 10-year review).										
PRAL Score Continuous form	112	179	0.04 (0.00 to 0.07)	0.05	-0.02 (-0.06 to 0.01)	0.20	112	179	0.00 (-0.02 to 0.03)	0.86
PRAL Score Categorical form										
-41.85 to 10.80	23	44	0.00 (Ref)		0.00 (Ref)				0.00 (Ref)	
10.81 to 17.44	31	49	-0.15 (-1.09 to 0.79)	0.75	-0.61(-1.71 to 0.50)	0.28	23	44	-0.04 (-0.86 to 0.78)	0.93
17.45 to 26.24	29	39	-0.23 (-1.28 to 0.81)	0.66	-0.82 (-2.04 to 0.40)	0.19	31	49	-0.39 (-1.27 to 0.49)	0.39
>26.24	29	47	1.03 (-0.40 to 2.45)	0.16	-0.60 (-2.08 to 0.88)	0.42	29	39	-0.19 (-1.25 to 0.88)	0.73
Test for trend:				0.34		0.33	29	47		0.53
NEAP Score Continuous form	112	179	**0.04 (0.01 to 0.07)**	**0.01**	0.01 (-0.02 to 0.04)	0.54	112	179	-0.00 (-0.03 to 0.02)	0.75
NEAP Score Categorical form										
15.15 to 58.35	25	47	0.00 (Ref)		0.00 (Ref)		25	48	0.00 (Ref)	
58.36 to 64.82	18	43	-0.26 (-1.20 to 0.68)	0.58	-0.82 (-1.89 to 0.25)	0.13	18	42	-0.86 (-1.70 to -0.03)	0.04
64.83 to 73.63	44	42	0.14 (-0.79 to 1.07)	0.77	0.20 (-0.87 to 1.27)	0.71	44	42	-0.63 (-1.45 to 0.19)	0.13
>73.63	25	47	0.81 (-0.31 to 1.93)	0.16	-0.21 (-1.38 to 0.95)	0.72	25	47	-0.65 (-1.54 to 0.25)	0.16
Test for trend:				0.15		0.81				0.20

*PRAL models were adjusted for total energy intake, dietary reporting, age, BMI and sex. NEAP models were adjusted for total energy intake, dietary reporting, age, and sex (box-cox; back transformed) linear mixed-effects models for repeated measures were used; results were then back-transformed and presented on their original scale at the mean of model covariates. N5 and N10 are the number of people in each category at the 5- and 10-year reviews, respectively. The same set of numbers applies to both depression and anxiety.

Table 3: Dietary acid load and subsequent 5-year change in outcome: the association between the diet acid indices at the 5-year review and change in depression, anxiety, fatigue from the 5- and 10-year reviews.

		Change in depression		Change in anxiety			Change in fatigue	
	N	**β*(95%CI)**	***p***	**β*(95%CI)**	***p***	**N**	**β*(95%CI)**	***p***
PRAL Score Continuous form	166	**0.07 (0.03 to 0.11)**	**<0.001**	0.01 (-0.04 to 0.06)	0.74	172	**0.04 (0.01 to 0.06)**	**0.01**
PRAL Score Categorical form								
-41.85 to 10.80	42	-1.60 (-2.38 to 0.81) (Ref)**		-0.67 (-1.70 to 0.36) (Ref)**		41	0.31 (-0.87 to 0.24) (Ref)**	
10.81 to 17.44	47	**+1.51 (0.39 to 2.63)**	**0.01**	+0.48 (-0.95 to 1.92)	0.51	49	+0.28 (-0.48 to 1.04)	0.47
17.45 to 26.24	35	**+1.45 (0.17 to 2.73)**	**0.03**	-0.34 (-1.99 to 1.31)	0.68	37	+0.50 (-0.37 to 1.36)	0.26
>26.24	42	**+3.01 (1.54 to 4.48)**	**<0.001**	+0.07 (-1.82 to 1.97)	0.94	45	**+1.16 (0.15 to 2.16)**	**0.02**
Test for trend:			**<0.001**		0.87			**0.03**
NEAP Score Continuous form	166	**0.07 (0.04 to 0.10)**	**<0.001**	0.02 (-0.02 to 0.06)	0.33	172	**0.03 (0.00 to 0.05)**	**0.03**
NEAP Score Categorical form								
15.15 to 58.35	46	-1.24 (-2.02 to -0.46) (Ref)**		-0.54 (-1.52 to 0.43) (Ref)**		46	-0.19 (-0.72 to 0.34) (Ref)**	
58.36 to 64.82	41	+0.75 (-0.39 to 1.89)	0.20	-0.34 (-1.78 to 1.10)	0.64	42	-0.09 (-0.86 to 0.69)	0.83
64.83 to 73.63	36	**+1.62 (0.44 to 2.80)**	**0.01**	+1.16 (-0.34 to 2.65)	0.13	39	+0.45 (-0.35 to 1.25)	0.26
>73.63	43	**+2.06 (0.92 to 3.20)**	**<0.001**	+0.39 (-1.06 to 1.84)	0.59	45	+0.44 (-0.34 to 1.22)	0.27
Test for trend:			**<0.001**		0.29			0.15

*PRAL models were adjusted for total energy intake, dietary reporting, age, BMI and sex. NEAP models were adjusted for total energy intake, dietary reporting, age, and sex.

**Results for categorical variables are presented as the mean absolute change (95% CI) of reference level of the predictor then mean change (95% CI) of other levels relative to reference (box-cox; back transformed) linear regression models were used; results were then back-transformed and presented on their original scale at the mean of model covariates.

Table 4: Multivariable models of the association between the diet acid index variables and depression, anxiety, fatigue at the 10-year review.

	N	Depression at 10-year review β*(95%CI)	*p*	Anxiety at 10-year review β*(95%CI)	*p*	Fatigue at 10-year review β*(95%CI)	*p*
PRAL Score Baseline	161	**0.10 (0.05, 0.16)**	**<0.001**	**0.11 (0.05, 0.17)**	**<0.001**	0.03 (-0.02, 0.07)	0.27
PRAL Score Change from baseline to 5-year review		**0.09 (0.03, 0.15)**	**<0.001**	**0.08 (0.01, 0.15)**	**0.02**	0.02 (-0.03, 0.07)	0.49
PRAL Score Change from 5- to 10-year review		**0.09 (0.04, 0.14)**	**<0.001**	**0.11 (0.05, 0.17)**	**<0.001**	0.03 (-0.02, 0.08)	0.17
NEAP Score Baseline	161	**0.09 (0.03, 0.16)**	**<0.001**	**0.11 (0.04, 0.17)**	**<0.001**	0.02 (-0.03, 0.07)	0.51
NEAP Score Change from baseline to 5-year review		**0.07 (0.01, 0.14)**	**0.03**	**0.07 (0.00, 0.15)**	**0.04**	-0.01 (-0.06, 0.05)	0.76
NEAP Score Change from 5- to 10-year review		**0.07 (0.02, 0.13)**	**0.01**	**0.10 (0.04, 0.16)**	**<0.001**	0.02 (-0.03, 0.06)	0.48

*PRAL and NEAP models were adjusted for total energy intake, dietary reporting, age, and sex.