# ADHERENCE TO A HEALTHY LIFESTYLE AND MULTIPLE SCLEROSIS: A CASE-CONTROL STUDY FROM THE UK BIOBANK

**Running head**: healthy lifestyle and MS

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# ABSTRACT

**Background:** Multiple sclerosis (MS) is a common and disabling condition. The importance of healthy lifestyle for this disease is poorly explored.

**Objective:** To test whether adherence to healthier lifestyle patterns is associated with a lower presence of multiple sclerosis (MS).

**Methods**: By using a case-control design, we investigated the combined association of four healthy lifestyle-related factors (no current smoking, healthy diet, exercising regularly, body mass index <30 kg/m2) and the prevalence of MS. A logistic regression analysis, adjusted for potential confounders, was used and data reported as odds ratios (ORs) with their 95% confidence intervals (CIs).

**Results**: 728 participants with MS were matched with healthy controls (n=2,912) using a propensity score approach. In a multivariate analysis, compared to those who scored low in the composite lifestyle score (0-1 healthy lifestyle factors), people who adopted all four low risk lifestyle factors showed a 71% lower odds of having MS (OR=0.29; 95% CI: 0.15-0.56). Moreover, there was a strong linear trend, suggesting that the higher number of healthy lifestyle behaviors was associated with lower odds of having MS.

**Conclusion**: Adopting a healthy lifestyle is associated with a lower prevalence of MS. This association should be explored further in cohort studies.

# INTRODUCTION

Multiple sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system (CNS) and the most common non-traumatic cause of disability in young adults, currently incurable. The incidence of MS is increasing worldwide, and environmental factors are considered critical player of this increase.[[1](#_ENREF_1)] Clinically MS is characterized by fully or partially reversible episodes of neurological symptoms (e.g. visual loss, limb weakness or sensory loss, ataxia) that over time can develop into a steadily progressive form eventually leading to impaired mobility and cognition, disability and poor quality of life.[[1](#_ENREF_1)] Together with its high socioeconomic impact, MS is associated with an elevated symptom burden, including pain, and a higher mortality rate compared to the general population.[[2](#_ENREF_2)]

Preclinical and epidemiological data suggest that diet, smoking and a sedentary lifestyle play an important role in the development and progression of MS.[[3](#_ENREF_3)] Obesity, especially during adolescence and childhood, is associated with an increased risk of developing MS later on in adult life.[[4](#_ENREF_4)] In contrast, calorie restriction (CR), intermittent fasting and diet-induced alterations of gut microbiome ameliorate the clinical course and pathology of the main MS animal model, experimental autoimmune encephalomyelitis (EAE).[[5](#_ENREF_5)] Regular exercise training may also exert a protective effect because of its metabolic, anti-inflammatory and neuroprotective actions.[[6](#_ENREF_6)] Smoking[[7](#_ENREF_7)], low serum levels of vitamin D[[8](#_ENREF_8)], and infection with the Epstein-Barr (EBS) virus[[9](#_ENREF_9)] are other factors that have been implicated in MS pathogenesis.

Given this background and the paucity of literature regarding healthy lifestyle factors and MS, in this large case-control study of men and women included in the UK Biobank, we examined the joint associations of different lifestyle factors with the a clinical diagnosis of MS. We hypothesized that nonobese individuals had the lowest prevalence of MS, particularly if normal weight was associated with regular exercise, a healthy diet, and no smoking.

# METHODS

## Study population

This research is covered by generic ethical approval from the NHS Research Ethics Committee (Ref. 11/NW/0382) for UK Biobank research. The analyses presented here were approved within project 41245 by the UK Biobank research committee on 03 May 2019. The data used for the aims of this paper were originally collected in 2007-2019. Briefly, the UK Biobank is a large health-focused resource, which specifically aims to understand the importance of environmental factors, genetics and lifestyle impact upon a broad array of health outcomes. The recruitment phase was conducted through a formal mail invitation, sent to 9.2 million households. Of them, more than 500,000 individuals attended UK Biobank assessment centers, to provide informed consent and complete baseline assessments. This process included touchscreen questionnaires, in-person interviews, and physical health examinations (full details for the UK Biobank’s assessment processes are available elsewhere).

## Exposure: healthy lifestyle-related factors

In agreement with the American Heart Association (AHA) guidelines[[10](#_ENREF_10)], we defined four healthy lifestyle factors, i.e. not currently smoking, healthy diet, body mass index (BMI) <30 kg/m2, and meeting the physical activity guidelines suggested for North American people. A healthy lifestyle score accounting for these behaviors was already used in the UK Biobank.[[11](#_ENREF_11)] Briefly, for constructing this score, the UK Biobank participants completed a questionnaire on their habitual dietary intake. To determine a categorical healthy diet variable for the purposes of our analysis, we used the UK Biobank’s dietary intake data on the consumption of fruit, vegetables, and fish and the consumption of processed meats and red meats. We defined a healthy diet as adherence to at least two of the healthy food items that include total fruit and vegetable intake, total fish intake, and a low intake of processed and red meat.[[11](#_ENREF_11)] Smoking status was defined in the UK Biobank as never, past, and current smokers and categorized for the aims of this work in yes/no. Physical activity was assessed with the International Physical Activity Questionnaires (IPAQ) short form.[[12](#_ENREF_12)] Based on the IPAQ scoring system, meeting the physical activity guidelines was defined as engaging in at least 150 minutes of moderate intensity activity weekly or 75 minutes of vigorous activity weekly.[[13](#_ENREF_13)]

Using the three criteria mentioned, a healthy lifestyle score was calculated ranging from 0 (no AHA criteria followed) to 4 (all followed).

## Outcome: multiple sclerosis definition

Prevalent MS in UK Biobank was based on medical history and linkage to data on hospital admissions. We used the MS variables provided by UK Biobank, with the ICD-10 (“G35”) indicating primary diagnoses. Details of the algorithms used to combine the data from different sources to identify MS have been described previously and are freely available on the UK Biobank website ([www.ukbiobank.ac.uk](http://www.ukbiobank.ac.uk)).

## Covariates

Data on several covariates were included in this work, including: age; sex; yearly income (categorized as < 18,000 £; 18,000 to 30,999 £; 31,000 to 51,999 £; 52,000 to 100,000 £; and > 100,000 £); country of birth (categorized as UK and non-UK); presence of diabetes, cancer, fractures, or other serious medical condition/disability; and alcohol intake (never, past, current).

## Statistical analysis

Given that MS is relatively rare in the population, we selected controls for MS cases in the UK Biobank matching on age (continuous variable) and sex (binary variable). Cases and controls were matched at a 1:4 ratio using the STATA MAHAPICK process, a multivariate matching procedure based on a Mahalanobis scoring algorithm. Study participants with incomplete covariates were removed before the matching to ensure all cases and controls have complete data. Participant characteristics were summarized by case and control status using means and standard deviation for age and body mass index, and frequencies and percentages for other variables. T-test or chi-squared test were used to assess differences in participants’ characteristics. Univariate and multivariate conditional logistic regression analyses were carried out to quantify the univariate associations between lifestyle factors and MS as well as with the adjustment of a range of covariates. Finally, we created a composite lifestyle score by summarizing the four examined lifestyle factors (healthy diet: 0 [AHA=0] vs. 1[AHA≥1]; BMI: 0 [BMI≥30 kg/m2 vs. 1 [BMI<30 kg/m2]; smoking: 0 [current smoker] vs. 1[not current smoking]; physical activity: 0 [IPAQ = low] vs. 1[IPAQ = moderate or high]). Due to the small number of “0” is the composite lifestyle score (n=1), composite lifestyle score “0” and “1” were collapsed into one category. This score was further used in univariate and multivariate logics regressions to examine the association of composite lifestyle with MS. Data were reported as odds ratios (ORs) with their 95% confidence intervals (CIs). For sensitivity analyses, we limited the modified composite lifestyle score to diet, smoking, and physical activity to evaluate its association to the prevalence of MS in each weight category defined by BMI (<25, 25- <30, ≥ 30 kg/m2). All statistical analyses were conducted in Stata 16.0 (StataCorp, Texas, USA)

# RESULTS

At the baseline evaluation of 502,536 participants initially included in the UK Biobank, 1,236 had a diagnosis of MS (prevalence=0.25%). After excluding observations with missing data on the relevant lifestyle factors for calculating the AHA lifestyle score or any of the covariates included in the fully-adjusted analyses, 728 participants with MS were finally included. These participants were matched using a propensity score approach of 1:4 with healthy controls (n=2,912).

As shown in **Table 1**, no significant differences in terms of age, sex or BMI were observed between cases and controls. People with MS had significantly lower income than the controls (p<0.0001), and a significantly higher prevalence of other medical conditions/disabilities. People with MS were less physically active, as shown by lower IPAQ scores (p<0.0001) (**Table 1**).

**Table 2** shows the multivariate logistic regression analyses investigating the association between the composite lifestyle score and the presence of MS. Compared to those who scored 0-1 on the composite lifestyle score (low adherence to healthy lifestyle), adherence to all three or four lifestyle factors was associated with a strong reduced odds of having MS (three healthy lifestyle factors: OR=0.32; 95% CI=0.16-0.63; p<0.001; four healthy lifestyle factors: OR=0.29; 95% CI: 0.15-0.56; p=<0.001). The association between the lifestyle score and the prevalence of MS appears to follow a dose-response relationship: the higher the number of healthy lifestyle behaviors, the lower the odds of having MS (P for trend < 0.001).

Other significant protective factors for the presence of MS were a high yearly income, whilst the presence of other serious medical conditions/disabilities and past smoking increased the odds of MS (**Table 2**).

**Figure 1** describes the association between the AHA lifestyle score with the prevalence of MS stratified by BMI categories. The association between healthy lifestyle and the prevalence of MS was not statistically significant in current smokers, whilst in the other strata we did not see any significant interaction.

# DISCUSSION

In this prevalent case-control study, including 728 participants with a diagnosis of MS matched with 2,912 healthy controls, we found that adherence to three or four healthy lifestyle-related factors is strongly and inversely associated with the diagnosis of MS, even after controlling for several potential confounders. People adherent to all four healthy lifestyle factors had a ~70% lower odds of MS than those who scored low in the composite lifestyle score. Results of our sensitivity analysis further indicated that combinations of healthy lifestyle factors were particularly powerful: the higher the number of healthy lifestyle behaviors, the lower the presence of MS. Our findings suggest that adopting a healthier lifestyle, including high levels of physical activity, healthier diets, avoiding obesity and smoking, may markedly reduce the risk of developing MS.

Several biologic mechanisms might explain these findings. MS is an immune-mediated disease with a strong inflammatory component, which is the main target of current disease-modifying therapies. These treatments which have changed MS natural history by reducing relapses, disability progression and accrual of new inflammatory lesions. [[1](#_ENREF_1),[14](#_ENREF_14)]. Obesity early in life is associated with increased risk to develop MS later on.[[15](#_ENREF_15)] Notably, obesity promotes chronic inflammation,[[16](#_ENREF_16)] while calorie restriction (CR) exerts a powerful antiinflammatory and antioxidant effect in animal models and humans as well.[[17](#_ENREF_17)] An improved adipokine profile associated with CR, including lower leptin and higher adiponectin levels may, at least in part, be responsible for the anti-inflammatory and improved T-cell immune responses beneficial to MS and its animal models.[[18](#_ENREF_18)] Modifications in diet quality, as in the fibre-rich Mediterranean diet, might potentiate the effects of weight loss in reducing inflammation and immune activation.[[19](#_ENREF_19)]

Another key mechanism through which a healthy diet may induce its beneficial effects involves alterations in the gut microbiota with an enrichment of short chain fatty acids (SCFA)-producing bacteria strains, such as the Lactobacillaceae, Bacteroidaceae, and Prevotellaceae families, which are known to have immunomodulatory and anti-inflammatory effects.[[20](#_ENREF_20)] In the EAE animal study, diet-induced microbial changes were accompanied by a reduction of IL-17 producing T cells and an increase in regulatory T cells in the gut lamina propria. Importanly, fecal microbiome transplantation experiments demonstrated that diet-induced EAE protection could be transferred by the gut microbiota.[[5](#_ENREF_5)]

Regular exercise training by reducing visceral adiposity and improving insulin sensitivity and glucose tolerance may also play an key role in reducing inflammation.[[21](#_ENREF_21)], Moreover, exercise training is know to increase parasympathetic activity,[[22](#_ENREF_22)] which through the activation of the cholinergic anti-inflammatory pathway dampens the macrophage secretion of TNFα, IL-1, and IL-18.[[23](#_ENREF_23)] Endurance exercise by increasing the production of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) may also prevent neural death and enhance neural regeneration and remyelination.[[24](#_ENREF_24)], Diet seems to have a similar effect.[[25](#_ENREF_25)]

Experimental data suggest that cigarette smoking may play a role in the development of MS.[[7](#_ENREF_7)] The risk of MS in smokers seems to be dose- and duration-dependent, suggesting causality.Individual with MS who smoke experience more disease activity, accelerated brain atrophy, and a higher disability burden.[[26](#_ENREF_26)]How smoking can induce MS is unclear. The toxic compounds produced during cigarette burning are known to activate the immune system and to induce local and systemic inflammation, which stimulates lymphocyte autoreactivity.[[27](#_ENREF_27)] Additional effects of cigarette smoke include disruption of the blood-brain barrier with increased influx of permeable solutes and direct neurotoxic effects.[[28](#_ENREF_28)] Cyanide, a toxic byproduct of cigarette smoke, causes demyelination in the central nervous system of animals, especially when repeated doses of cyanide are administered.[[29](#_ENREF_29)]

The role of diet and other healthy lifestyle factors in modulating MS clinical progression has previously been explored. For example, it has been reported that dietary factors may exacerbate or improve MS symptoms both in relapsing-remitting MS and in primary-progressive MS.[[30](#_ENREF_30)] Moreover, a large cross-sectional study including almost 7,000 people with MS found that following a healthy diet was associated with less disability and symptom burden.[[3](#_ENREF_3)] In a small study, a multimodal intervention for improving lifestyle in people affected by MS was able to improve quality of life and mental health over 3 years of follow-up.[[31](#_ENREF_31)] Altogether, these evidences support the importance of a healthy lifestyle in MS.

The findings of our study should be interpreted considering also its limitations. First, the most important, is the design of our study, i.e. a case-control design that can introduce the relevant problem of reverse causality. The older age of the participants with MS, for example, needs to be clearly noted since it is possible that many of these cases have had MS for many years and, for example, low physical activity. Even though the present study matched for several potential factors and adjusted for different covariates, reverse causation cannot be ruled out. Healthy controls are able to eat better and to be more physically active than MS patients who can experience mobility and eating problems.[[30](#_ENREF_30)] For example, It was reported that people with MS, at least at the beginning, tend to improve their diet.[[32](#_ENREF_32)] This in itself is an important consideration for further research, and raises the possibility that the elevated rates of mortality from cardiovascular and metabolic diseases observed among people with MS[[33](#_ENREF_33)] may be attributed to MS-specific barriers to adopt healthy lifestyle factors. However, previous case-control studies have also reported that healthy dietary patterns are associated with a reduced presence of a first clinical demyelinating event (rather than in people with established MS), which provides support for healthy dietary patterns playing a causal role in MS risk.[[34](#_ENREF_34)] A further limitation of our study is that the diagnosis of MS was made through medical history linked to data on hospital admissions, and not with the McDonald criteria that include clinical, biohumoral and imaging evidence contrary to our data based on clinical information.[[35](#_ENREF_35)] Finally, another important limitation could be the possible selection bias due to the limited sample size included due to the presence of missing data in almost half of the population.

In conclusion, our findings support the beneficial effect of adopting a healthy lifestyle in the prevention of MS since people with a higher adherence to the AHA criteria (i.e. healthier diets, physical activity, avoidance of obesity and no smoking) reported a lower prevalence of MS, even after taking into account several potential confounders. Future longitudinal studies are warranted to confirm these findings in order to support the use of lifestyle interventions for the prevention of MS.

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**Data availability statement**: The data that support the findings of this study are available at https://www.ukbiobank.ac.uk/, reference number [ID= 41245]. These data were derived from the following resources available in the public domain: <https://www.ukbiobank.ac.uk/>.

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# Table 1. Descriptive characteristics of the cases (multiple sclerosis) and healthy controls

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameter** | **MS (n=728)** | **Controls (n=2912)** | **p-value** |
| **Mean age (years) (SD)** | 53.9 (7.5) | 53.9 (7.5) | 0.99 |
| **Female sex (%)** | 28.7 | 28.7 | 0.99 |
| **BMI (kg/m2) (SD)** | 26.8 (5.1) | 27.0 (4.7) | 0.20 |
| **Yearly income > 100000 £ (%)** | 3.9 | 9.2 | <0.0001 |
| **UK native (%)** | 95.2 | 94.2 | 0.28 |
| **Diabetes mellitus (%)** | 3.4 | 2.0 | 0.02 |
| **Cancer** | 8.7 | 8.7 | 0.98 |
| **Fractures (%)** | 12.4 | 5.9 | <0.0001 |
| **Other serious medical condition/disability** | 86.8 | 19.2 | <0.0001 |
| **High IPAQ score (%)** | 23.9 | 37.6 | <0.0001 |
| **Current smokers (%)** | 15.8 | 12.5 | <0.0001 |
| **Current drinkers (%)** | 90.1 | 91.0 | 0.118 |

**Abbreviations**: BMI: body mass index; IPAQ: International Physical Activity Questionnaires

# Table 2. Multivariate logistic regression analysis

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameter** | **OR** | **low 95% CI** | **high 95% CI** | **p** |
| **Composite Lifestyle score (0-1) (n=84)** | Ref. |  |  |  |
| **2 (n=426)** | 0.5785 | 0.2855 | 1.1719 | 0.12862 |
| **3 (n=1218)** | 0.3184 | 0.1616 | 0.6274 | 0.00094 |
| **4 (n=1912)** | 0.2856 | 0.1456 | 0.5600 | 0.00027 |
| **Yearly income < 18000 £** | Ref. |  |  |  |
| **18000 to 30999 £** | 0.3574 | 0.2614 | 0.4885 | <0.0001 |
| **31000 to 51999 £** | 0.6650 | 0.4870 | 0.9081 | 0.01026 |
| **52000 to 100000 £** | 0.4581 | 0.3275 | 0.6407 | 0.00001 |
| **> 100000 £** | 0.5313 | 0.3106 | 0.9088 | 0.02093 |
| **Country of birth** | Ref. |  |  |  |
| **non-UK** | 0.8683 | 0.5363 | 1.4060 | 0.56588 |
| **Diabetes** | Ref. |  |  |  |
|  | 1.8164 | 0.9176 | 3.5955 | 0.08670 |
| **Cancer** | Ref. |  |  |  |
|  | 0.5896 | 0.4058 | 0.8567 | 0.00558 |
| **Fracture** | Ref. |  |  |  |
|  | 1.3262 | 0.9353 | 1.8806 | 0.11310 |
| **Other serious medical condition/disability** | 1.0000 |  |  |  |
|  | 36.3770 | 28.0386 | 47.1951 | <0.0001 |
| **No alcohol**  | Ref. |  |  |  |
| **past** | 0.7715 | 0.3873 | 1.5366 | 0.46046 |
| **current** | 1.5032 | 0.8472 | 2.6671 | 0.16353 |

**Abbreviations:** BMI: body mass index; IPAQ: International Physical Activity Questionnaires; OR: odds ratio; CI: confidence intervals.

**Notes**: all data are reported as ORs (odds ratios) with their 95% confidence intervals (CIs), derived for the multivariable model of each of the factors adjusted for the others in the model.

# FIGURE LEGEND

**Figure 1. Association between lifestyle score with the prevalence of MS stratified by BMI categories, smoking status, physical activity leven and dietary score**

**Abbreviations:** AHA: American Heart Association;BMI: body mass index; IPAQ: International Physical Activity Questionnaires.

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **Case/Control** | **Odds ratio (95% CI)** |
|  |  |  |  |
| **BMI <25** | 25/19 | Reference |
| 2 vs. 0-1 | 131/226 | 0.32 (0.13 to 0.75) |
| 3 vs. 0-1 | 140/895 | 0.18 (0.07 to 0.38) |
|  |  |  |
| **BMI 25-30** | 27/28 | Reference |
| 2 vs. 0-1 | 106/304 | 0.14 (0.05 to 0.33) |
| 3 vs. 0-1 | 142/735 | 0.15 (0.06 to 0.35) |
|  |  |  |
| **BMI > 30** | 17/62 | Reference |
| 2 vs. 0-1 | 73/259 | 0.41 (0.17 to 0.99) |
| 3 vs. 0-1 | 67/384 | 0.19 (0.08 to 0.45) |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |  |
| **Never Smoker** | 48/151 | Reference |
| 2 vs. 0-1 | 147/571 | 0.43 (0.26 to 0.70) |
| 3 vs. 0-1 | 160/1106 | 0.43 (0.27 to 0.71) |
|  |  |  |
| **Past Smoker** | 30/64 | Reference |
| 2 vs. 0-1 | 106/131 | 0.56 (0.24 to 1.31) |
| 3 vs. 0-1 | 112/524 | 0.26 (0.12 to 0.56) |
|  |  |  |
| **Current Smoker** | 18/55 | Reference |
| 2 vs. 0-1 | 46/98 | 1.28 (0.43 to 0.38) |
| 3 vs. 0-1 | 51/212 | 0.58 (0.19 to 1.72) |
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| **IPAQ=Low** | 22/62 | Reference |
| 2 vs. 0-1 | 105/211 | 0.66 (0.23 to 1.83) |
| 3 vs. 0-1 | 171/288 | 0.20 (0.07 to 0.59) |
|  |  |  |
| **IPAQ=moderate** | 12/44 | Reference |
| 2 vs. 0-1 | 85/361 | 0.44 (0.17 to 1.12) |
| 3 vs. 0-1 | 159/851 | 0.58 (0.24 to 1.39) |
|  |  |  |
| **IPAQ=High** | 3/51 | Reference |
| 2 vs. 0-1 | 48/265 | 1.29 (0.34 to 4.88) |
| 3 vs. 0-1 | 123/779 | 1.59 (0.41 to 5.43) |
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| **AHA score = 0-1** | 55/202 | Reference |
| 2 vs. 0-1 | 123/394 | 0.75 (0.45 to 1.26) |
| 3 vs. 0-1 | 88/438 | 0.91 (0.53 to 1.56) |
|  |  |  |
| **AHA score = 2** | 50/43 | Reference |
| 2 vs. 0-1 | 129/386 | 0.16 (0.08 to 0.30) |
| 3 vs. 0-1 | 141/827 | 0.15 (0.08 to 0.28) |
|  |  |  |
| **AHA score = 3** | 21/79 | Reference |
| 2 vs. 0-1 | 53/148 | 1.18 (0.43 to 3.21) |
| 3 vs. 0-1 | 68/395 | 0.25 (0.09 to 0.69) |
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