Published Ahead of Print on October 25, 2021 as 10.1212/WNL.0000000000012957

Neurology®
The most widely read and highly cited peer-reviewed neurology journal
The Official Journal of the American Academy of Neurology

AMERICAN ACADEMY OF NEUROLOGY®

Neurology Publish Ahead of Print
DOI: 10.1212/WNL.0000000000012957

Association of Body Mass Index in Adolescence and Young Adulthood and Long-term Risk of Multiple Sclerosis: A Population-Based Study

Author(s):
Rune A. Aa. Høglund, MD, PhD[1]; Haakon E. Meyer, MD, dr.med.[2, 3]; Hein Stigum, Dr. philos.[2, 3]; Øivind Torkildsen, MD, PhD[4, 5]; Nina Grytten, PhD[4, 6]; Trygve Holmøy, MD, PhD[1, 7]; Ola Nakken, MD, PhD[1]

Corresponding Author:
Rune A. Aa. Høglund
r.a.hoglund@medisin.uio.no

Affiliation Information for All Authors: 1 Department of Neurology, Akershus University Hospital, Lørenskog, Norway; 2 Norwegian Institute of Public Health, Oslo, Norway;3 Department of Community Medicine and Global Health, University of Oslo, Oslo, Norway; 4 Department of Clinical Medicine, University of Bergen, Bergen, Norway;5 Neuro-SysMed, Department of Neurology, Haukeland University Hospital, Bergen, Norway; 6 Norwegian Multiple Sclerosis Competence Centre, Department of Neurology, Haukeland University Hospital, Bergen, Norway;7 Institute of Clinical Medicine, University of Oslo, Oslo, Norway;

Contributions:
Rune A. Aa. Høglund: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Haakon E. Meyer: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Hein Stigum: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Øivind Torkildsen: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Nina Grytten: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data; Additional contributions: Generating figures
Trygve Holmøy: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data
Ola Nakken: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data; Additional contributions: Generating figures.

Number of characters in title: 132

Abstract Word count: 203

Word count of main text: 2862

References: 41

Figures: 3

Tables: 3

Supplemental: 1. eTable 1 2. eTable 23. eTable 3 4. Ethical board approval for informed consent waiver (Not intended to be published)5. STROBE Checklist 6. Response to reviewers in PDF format7. Manuscript with highlighted changes

Statistical Analysis performed by: Professor Hein Stigum, dr.philos (Co-author), Institute of health and society, University of Oslo Ola Nakken, MD PhD, Department of Neurology, Akershus University Hospital

Search Terms: [41] Multiple sclerosis, [54] Cohort studies, [57] Incidence studies, [59] Risk factors in epidemiology, [132] Autoimmune diseases

Acknowledgements: The authors acknowledge the cohorts participants.

Study Funding: Rune A. Høglund is funded by a grant from the South-Eastern Norway regional health authority (Grant 2020005).

Disclosures: R. A. Aa. Høglund is funded by a grant from the South-Eastern Norway regional health authority (Grant 2020005); H.E.Meyer reports no disclosures relevant to the manuscript; H.Stigum reports no disclosures relevant to the manuscript; Ø.Torkildsen reports no disclosures relevant to the manuscript; N. Grytten reports no disclosures relevant to the manuscript; T. Holmøy reports no disclosures relevant to the manuscript; O. Nakken reports no disclosures relevant to the manuscript.

Abstract

Objective:
To prospectively investigate the long-term relationship between body mass index (BMI) in adolescents and young adults, and risk for multiple sclerosis (MS) at population level.

Methods:
We utilized data from the population-based compulsory Norwegian tuberculosis screening program during 1963-1975, including objectively measured height and weight from approximately 85% of all eligible citizens. This was combined with data from the Norwegian MS registry and biobank up to November 2020. BMI was standardized according to age and sex, and risk for MS was calculated using Cox proportional hazard models.

Results:
During 30,829,506 years of follow-up we found 1,409 cases of MS among 648,734 participants in eligible age groups (14-34 years). Overall, obesity was associated with increased MS risk (HR 1.53 [95% CI 1.25-1.88]), and the risk was similar in men (HR 1.4 [95% CI 0.95-2.06] and women (HR 1.59 [95% CI 1.25-2.02]). Risk was highest for the youngest age groups (age 14-16: HR 1.73 [95% CI 1.19-2.53], 17-19: HR 1.61 [95% CI 1.08-2.39] and 20-24: HR 1.56 [95% CI 1.04-2.36]) and was no longer present for those older than 30 years.

Conclusion:
High BMI in individuals aged 14 to 24 years was associated with increased MS-risk later in life, in both males and females.

1 Introduction

Multiple sclerosis (MS) is a chronic, inflammatory and demyelinating disease of the central nervous system (CNS), commonly affecting young adults [1]. While the number of available treatments have expanded in the last decade [2], no cure is available. Knowledge of risk factors for acquiring MS remain an important aspect for future disease prevention or improved therapies.

Numerous risk factors have been identified, including a comprehensive map of genes involved in mainly immune system functions [3]. Additionally, several environmental factors have been implied. This includes previous infection by Epstein Barr Virus [4, 5], as well as Vitamin D, smoking and obesity [6].

Like for most observational studies on lifestyle and environmental risks, the association between obesity and MS risk has been difficult to establish, mainly due to data shortcomings. Identifying whether age at the time of obesity influences risk is additionally relevant for taking preventive

action. Previous observational studies have suggested childhood and adolescence as such susceptibility ages. Two studies have been prospective and based on objective measures [7, 8], however these were restricted to children aged 7 to 13 years and males under the age of 19 years respectively. Other studies have in large been based on self-reported and retrospective measures of weight and body silhouettes, where information bias cannot be excluded [9-13]. Finally, the effect of obesity has been inconsistently reported in males, likely due to underpowered studies [6].

Using a large, mandatory health screening where anthropometrics in near all citizens were objectively measured, we here aim to investigate the long-term relationship between body mass index (BMI), age and MS risk in a population-based and prospective manner.

2 Materials and Methods

2.1 Study population and case ascertainment

In the period 1963-1975, a mandatory national screening program for tuberculosis included Norwegian citizens aged 14 years and older in 18 of Norway's 19 counties, with an attendance rate of approximately 85% [14]. Nonattendance was mainly due to "acceptable excuses", such as already diagnosed with tuberculosis, in military service, or in hospital. In addition to demographic data, x-ray findings, vaccination status and results from tuberculin skin tests, screening included objective measures of weight and height, collected according to standardized protocols, without shoes and clothing (except undergarments in females) above the waist.

For this investigation, we excluded individuals aged less than 14 (who only attended when considered high tuberculosis risk) or more than 34 years (low number of MS outcomes), those with missing or implausible BMI (>60), possible tuberculosis (based on chest x-ray findings and BCG vaccine status), MS symptom onset prior to screening, resulting in a study population of 648,768 individuals (Figure 1), from 1,910,824 screening participants. If participants had more than one BMI measurement, the first was selected.

We retrieved vital status and emigration from the National Population Registry.

In our main analyses, including sensitivity analyses, MS cases were ascertained through the Norwegian MS- registry and biobank (from here referred to as "the MS-registry"). The MS registry is based on informed consent. Its operative period dates back to 2001. While being a nationwide registry, in adjacent years following registry initiation, geographical coverage was variable. The completeness of the registry has gradually increased and is currently reported being 70% of that calculated from an administrative health register (Norwegian Patient Registry) and reaches 80 to 90 % in Telemark and Hordaland counties [15, 16]. Cases are registered in the database by local neurologists upon diagnosis (incident cases) or retrospectively based on hospital records and patient recall (prevalent cases). From the MS registry we collected information on date of symptom onset, date of diagnosis, disease course at diagnosis and county of residence.

Patients who died before or shortly after 2001 could not be included in the MS registry due to lack of consent. To assess the association between BMI and MS risk in an independent patient cohort we performed a separate analysis where cases were ascertained through the Norwegian Cause of Death Registry, excluding cases also found in the MS registry. We searched all death certificates from 1963 to 2020 containing codes corresponding to MS at any level of cause of death, using the following international classification of diseases (ICD) codes; ICD 7 (1963-1968): 345, ICD 8 and 9 (1969-1995): 340, ICD 10 (1996 onwards): G35. To minimize the risk of including cases with MS at date of BMI

measurement we restricted this analysis to participants aged 19 years or younger at tuberculosis screening [17].

Data was extracted on 26th of November 2020. Register linkage was facilitated through the unique personal identification number given to all Norwegian citizens.

2.2 Modelling BMI

Whereas BMI (kg/m^2) defines obesity and overweight similarly for males and females in adults, BMI varies with age and sex in growing children. To standardize anthropometric measures across age-groups, we therefore modelled BMI in two different ways: 1. We used age -and sex-specific z-scores (standard deviation scores) calculated within the dataset and created both a continuous variable (one unit z-score steps) and a predefined categorical variable of underweight (z-score<-1), normal weight (z-score from -1 to 0.99), overweight (z-score from 1 to 1.99) and obesity (z-score≥2). Z-scores are generally used for individuals aged less than 20. However, there is no obvious reason why this BMI transformation cannot be used also among older individuals. Hence, we calculated z-scores across all ages in order to have a homogenous exposure variable. 2. We modelled BMI in all age groups with percentiles of distribution standardized within the dataset by age (one-year groups for ages <20, 5-year groups for ages ≥20) and sex. Here, we defined underweight as BMI <10 percentile, normal weight as BMI in the 10-84 percentile, overweight as BMI in the 85-94 percentile and obese as BMI ≥95 percentile.

2.3 Statistical analysis

Each participant contributed follow-up time from the date of BMI measurement to the date of MS symptom onset, death, emigration, or the end of study follow-up (November 26th, 2020), whichever came first.

Hazard ratios (HR) and their 95 % confidence intervals (CI) were calculated using Cox proportional hazard models with attained age (age at exposure + time since exposure) as time variable. Age at screening, sex (except in sex-specific analyses), birth year and county of residence were used as covariates in the models. Between sexes heterogeneity was tested using a likelihood ratio test between the basic model and a model including an interaction term of BMI percentiles and sex.

To investigate the possibility of particular susceptibility ages, we compared a model including BMI percentile categories and age at screening, with a model including an interaction term. Comparison was tested with a likelihood ratio test. We further predicted and plotted the hazard ratio for MS according to obesity before MS onset across different ages using a flexible parametric model [18]. Here, both obesity (binary variable constructed from percentile categories) and age at screening were modelled using cubic splines, including an interaction term between them.

To minimize the possibility of including participants with height and weight measured in a prodromal phase of MS [19], we conducted a sensitivity analysis using percentile categories where the first 5 years of follow up were excluded.

To assess the effect of potential bias from incomplete case finding in the MS registry, we performed a second sensitivity analysis using percentile categories, restricting data to residents from Hordaland and Telemark.

For the independent patient cohort identified by the Norwegian Cause of Death Registry, HR were calculated using Cox proportional hazard models specified the same way as described above. Here,

participants contributed follow-up time from the date of BMI measurement to the date of MS related death, death from other causes, emigration or the end of study follow-up (November 26th, 2020).

Tests of proportional hazards did not reveal any violations of the assumption. Values of $p<0.05$ were considered statistically significant. The statistical program STATA was used for calculations.

2.4 Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the regional ethics committee (REK South East, ref no 2016/1731), with informed consent for patients included from the National tuberculosis screening program waived in the current study. Patients included from the MS registry had given their written and oral consent to registry inclusion and no additional consent was acquired for this project.

2.5 Data availability

Data from the Norwegian MS registry and biobank may be acquired by application to the registry [20]. Data from the screening program for tuberculosis may be obtained by application to the National Institute of Public Health (NIPH, Norway) [21].

3 Results

3.1 Cohort description

648,768 individuals with a mean follow-up time of 47.5 (SD 8.1) years yielded a total of 30,829,506 years of observation. We identified 1,409 cases with MS in the MS- registry, with mean follow up among cases being 20.3 (SD 10.7) years. Of these, 429 (30 %) were male and 980 (70%) female. The baseline weight distributions among subjects who later did/did not develop MS are shown in Table 1. There were generally fewer identified MS cases among those screened at ages 20 and above, with very few obese and overweight cases identified in those over 30 years (Table 2 and 3).

3.2 MS risk

Overall, obesity (BMI ≥ 95% percentile) before MS debut was associated with increased MS risk (HR 1.53 (95% CI 1.25-1.88)) (Figure 2). An association between weight classes and MS risk was similar in males as females (test for sex interaction yielded p=0.53), regardless the method of standardizing weight classes.

Transforming BMI into standard deviation scores (z-scores), we found that a stepwise increase in BMI z-score at screening was associated with increased MS risk among all age groups except in those ≥30 years at screening (Table 2).

There was limited evidence that the effect of increased body weight on MS risk differed across ages (p=0.09). A tendency was observed that the risk increase was highest if obesity occurred earlier in life, than later (Figure 3). This pattern was most clear when using age and sex-standardized percentiles (Table 3), but should be interpreted carefully as there were relatively few identified MS cases among those aged 30 years or more at the date of BMI measurement. Interestingly, being underweight at the age of 14-16 years, was associated with reduced risk for MS (HR 0.62 (95% CI 0.42-0.91) using z-score categories and HR 0.54 (95% CI 0.34-0.87) using percentile categories) (Table 2 and 3).

In a sensitivity analysis excluding the first 5 years of follow up after BMI screening, results remained similar. This analysis comprised 646,527 cohort participants and 1305 MS cases. Overall HR for MS was 1.14 (95% CI 0.96-1.36) among overweight and 1.60 (95% CIs 1.30-1.97) among obese. The association between weight classes and MS risk was still most apparent in the youngest age group (eTable 1 [https://doi.org/10.5061/dryad.q2bvq83jr]).

In another sensitivity analysis restricted to the 100,444 participants and 292 MS cases from the two counties with highest MS registry coverage (Hordaland and Telemark), the association between MS and obesity persisted (eTable 2 [https://doi.org/10.5061/dryad.q2bvq83jr]).

Similar results were also found when using the Norwegian Cause of Death Registry for case ascertainment (eTable 3 [https://doi.org/10.5061/dryad.q2bvq83jr]). Among those 224,164 participants aged 14 to 19 years at tuberculosis screening, 219 MS cases were identified in the Norwegian Cause of Death Registry, but not in the MS Registry. HR (95% CI) for MS-associated death was 1.89 (1.19-3.01) among obese.

4 Discussion

This population-based study shows that being overweight or obese is associated with increased risk for MS diagnosis in both males and females. The unique cohort under study, where anthropometrics in near all citizens were measured in a standardized and objective manner, provides robust results. The age range at BMI screening is extensive, and we demonstrate that excessive weight is associated with later risk of MS, from adolescence into young adulthood.

While our study indicates that the window of MS susceptibility due to increased body weight is wide, the strongest association was seen in the youngest age group. Moreover, the stability of BMI tracking across age-groups is high [22] indicating that successful weight control at an early age could be of particular importance to reduce the risk of MS later in life.

Obesity and low vitamin D status are both identified as potentially modifiable risk factors in MS [6]. As BMI is associated with vitamin D status it has been a challenge to investigate them independently [23, 24]. A Mendelian randomization study found vitamin D and genetically determined childhood obesity are independent risk factors for MS [25]. As we did not have measurements of vitamin D, our study could not clarify whether these risk factors indeed are independent. It remains uncertain whether appropriate serum vitamin D could mediate the effects of obesity on MS risk. The association between high BMI and MS risk could theoretically also depict reverse causation, where yet undiagnosed disease results in inactivity and obesity in those affected. Together with Mendelian randomization studies [25, 26], our study with long term follow up, use of symptom onset instead of date of diagnosis, and consistent results when using lagged entry, does not support this theory. In fact, some studies rather suggests that prevalent MS disease is associated with weight loss [12, 27].

Obesity, like most of the other known environmental risk factors for MS, have implied effects on the immune system [28]. Presence of both high BMI (>27 kg/m^2) and the risk gene human leukocyte antigen (HLA)-DRB1*15:01, significantly increase risk for MS more than the independent risk contributions, suggesting interaction [29]. While the exact role of obesity in increasing the risk is still unknown, it has been shown that MS patients with high BMI has higher levels of proinflammatory cytokine IL-6 and also leptin in the cerebrospinal fluid, as well as higher clinical disability, indicating inflammation and obesity interact [30]. MS is just one of many auto-immune diseases associated with obesity, systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), rheumatoid and psoriatic arthritis and thyroid autoimmunity are among others [31]. Imbalance in form of increased pro- and reduced anti-inflammatory adipokines secreted in obese may participate in generation of such

risk, and the reverse could also potentially explain the risk reduction we observe among underweight individuals [32, 33].

This study has strength in being a large, prospective population study with a broad age distribution and long follow up. Our BMI- data was retrieved from objective and standardized measurements of height and weight in a compulsory health screening [14]. Except from a Norwegian male conscription cohort [8] and a Danish cohort of school children [7], previous studies have in large been based on retrospective, self-reported anthropometric measures of either weight, BMI or selection from a range of body silhouettes [9-13]. The precision of such measures may be weak. Moreover, it has been shown that biases in self-reported height and weight measurements are not randomly distributed and therefore cannot be easily corrected [34]. As such, bias in self reporting of anthropometric measures has been associated with body composition and lifestyle factors with a somewhat different pattern between sexes [34-36].

Our study has limitations. While the diagnosis of MS in the MS- registry is likely to be correct and constantly being updated, registry coverage for our study population still is incomplete and may have differed throughout the study period. It has been reported that overweight is associated with more rapid disability progression and early death [37, 38]. Missing MS patients dying before possible MS registry capture could therefore impact our results. While both incomplete registration and missing information on disease incidence limits MS mortality data, concordant HRs when using cases uniquely identified through the Norwegian Cause of Death Registry argues against the possibility of bias from non-ascertainment of deceased MS patients. Incomplete MS registry coverage may however relate to BMI in other unknown ways, and bias due to missing data and unmeasured confounders cannot be excluded. Still, consistent results in our sensitivity analysis using two counties characterized by more adequate case finding suggest confounding from incomplete case ascertainment is a minor problem.

Smoking may be a risk factor for MS [6], and smoking is associated with BMI. Although we have not adjusted for smoking in our analysis, it is unlikely that this has substantially biased our results. First, the effect of excessive weight on MS risk was greatest in the age group between 14-16, where smoking was less prevalent compared to older age groups [39]. Second, smokers are generally leaner than non-smokers [40]. If smoking confounds our results in any way, it should therefore again bias results towards the null, hence resulting in an under-estimation of the effects seen in this study. Neither the national screening program for tuberculosis nor the Norwegian MS registry and biobank includes complete data on other risk factors associated with MS, including EBV or HLA status, that may interact with obesity in risk for MS [28]. Further studies are required to address and disentangle such potentially associated risk factors.

In conclusion, this is to date the most robust population-based study on MS risk due to excess weight, showing a consistent increased risk if obese during adolescence and persisting into young adulthood. The prevalence of MS has increased dramatically during the last decades in the US and Europe [41] and our results suggest that this could partly be due to the corresponding world-wide obesity epidemic occurring in young adults.

References

1. Filippi M, Bar-Or A, Piehl F, et al. Multiple sclerosis. Nature Reviews Disease Primers 2018;4:43. doi: 10.1038/s41572-018-0041-4.
2. Tintore M, Vidal-Jordana A, Sastre-Garriga J. Treatment of multiple sclerosis - success from bench to bedside. Nat Rev Neurol 2019;15:53-58. doi: 10.1038/s41582-018-0082-z.
3. Consortium IMSG. Multiple sclerosis genomic map implicates peripheral immune cells and microglia in susceptibility. Science (New York, NY) 2019;365:eaav7188. doi: 10.1126/science.aav7188.
4. Ascherio A, Munger KL. Environmental risk factors for multiple sclerosis. Part I: the role of infection. Annals of neurology 2007;61:288-299. doi: 10.1002/ana.21117.
5. Ascherio A, Munger KL. EBV and Autoimmunity. In: Münz C, ed. Epstein Barr Virus Volume 1: One Herpes Virus: Many Diseases. Cham: Springer International Publishing, 2015: 365-385.
6. Ascherio A, Munger KL. Epidemiology of Multiple Sclerosis: From Risk Factors to Prevention—An Update. Semin Neurol 2016;36:103-114. doi: 10.1055/s-0036-1579693.
7. Munger KL, Bentzen J, Laursen B, et al. Childhood body mass index and multiple sclerosis risk: a long-term cohort study. Multiple sclerosis (Houndmills, Basingstoke, England) 2013;19:1323-1329. doi: 10.1177/1352458513483889.
8. Cortese M, Riise T, Bjørnevik K, Myhr K-M. Body size and physical exercise, and the risk of multiple sclerosis. Multiple Sclerosis Journal 2018;24:270-278. doi: 10.1177/1352458517699289.
9. Gianfrancesco MA, Acuna B, Shen L, et al. Obesity during childhood and adolescence increases susceptibility to multiple sclerosis after accounting for established genetic and environmental risk factors. Obes Res Clin Pract 2014;8:e435-447. doi: 10.1016/j.orcp.2014.01.002.
10. Hedstrom AK, Olsson T, Alfredsson L. High body mass index before age 20 is associated with increased risk for multiple sclerosis in both men and women. Multiple sclerosis (Houndmills, Basingstoke, England) 2012;18:1334-1336. doi: 10.1177/1352458512436596.
11. Hedström AK, Olsson T, Alfredsson L. Body mass index during adolescence, rather than childhood, is critical in determining MS risk. Multiple Sclerosis Journal 2015;22:878-883. doi: 10.1177/1352458515603798.
12. Munger KL, Chitnis T, Ascherio A. Body size and risk of MS in two cohorts of US women. Neurology 2009;73:1543-1550. doi: 10.1212/WNL.0b013e3181c0d6e0.
13. Wesnes K, Riise T, Casetta I, et al. Body size and the risk of multiple sclerosis in Norway and Italy: the EnvIMS study. Multiple sclerosis (Houndmills, Basingstoke, England) 2015;21:388-395. doi: 10.1177/1352458514546785.
14. Waaler HT. Height. Weight and Mortality The Norwegian Experience. Acta Medica Scandinavica 1984;215:1-56. doi: 10.1111/j.0954-6820.1984.tb12901.x.
15. Aarseth J, Smedal T, Skår AB, Wergeland S. Årsrapport 2019 [Annual report 2019]: NORSK MULTIPPEL SKLEROSE REGISTER OG BIOBANK, 2020.
16. National Multiple Sclerosis competence center Norway. eRapport [eReport] 2020 [online]. Updated: 31.01.2021. Available at: https://forskningsprosjekter.ihelse.net/senter/rapport/NK-HB4/2020. Accessed 01.05.2021.
17. Yeshokumar AK, Narula S, Banwell B. Pediatric multiple sclerosis. Current opinion in neurology 2017;30:216-221. doi: 10.1097/wco.0000000000000452.
18. Royston P, Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. Stat Med 2002;21:2175-2197. doi: 10.1002/sim.1203.
19. Bjornevik K, Munger KL, Cortese M, et al. Serum Neurofilament Light Chain Levels in Patients With Presymptomatic Multiple Sclerosis. JAMA Neurol. 2020 Jan 1;77(1):58-64. doi: 10.1001/jamaneurol.2019.3238.

20. Norwegian MS Registry and Biobank. Søke tilgang til data [Applying for data access] [online]. Updated: 20.02.2020. Available at: https://helse-bergen.no/norsk-ms-register-og-biobank/soke-tilgang-til-data#retningslinjer. Accessed 20.05.2020.
21. Norwegian National Institute of Public Health. How to apply for access to data [online]. Updated: 20.12.2019. Available at: https://www.fhi.no/en/more/access-to-data/applying-for-access-to-data/. Accessed 20.05.2020.
22. Bayer O, Krüger H, von Kries R, Toschke AM. Factors associated with tracking of BMI: a meta-regression analysis on BMI tracking. Obesity (Silver Spring) 2011;19:1069-1076. doi: 10.1038/oby.2010.250.
23. Pereira-Santos M, Costa PR, Assis AM, Santos CA, Santos DB. Obesity and vitamin D deficiency: a systematic review and meta-analysis. Obes Rev 2015;16:341-349. doi: 10.1111/obr.12239.
24. Tønnesen R, Hovind PH, Jensen LT, Schwarz P. Determinants of vitamin D status in young adults: influence of lifestyle, sociodemographic and anthropometric factors. BMC Public Health 2016;16:385. doi: 10.1186/s12889-016-3042-9.
25. Jacobs BM, Noyce AJ, Giovannoni G, Dobson R. BMI and low vitamin D are causal factors for multiple sclerosis: A Mendelian Randomization study. Neurology(R) neuroimmunology & neuroinflammation 2020;7. doi: 10.1212/nxi.0000000000000662.
26. Mokry LE, Ross S, Timpson NJ, Sawcer S, Davey Smith G, Richards JB. Obesity and Multiple Sclerosis: A Mendelian Randomization Study. PLoS Med 2016;13:e1002053. doi: 10.1371/journal.pmed.1002053.
27. Dardiotis E, Tsouris Z, Aslanidou P, et al. Body mass index in patients with Multiple Sclerosis: a meta-analysis. Neurol Res 2019;41:836-846. doi: 10.1080/01616412.2019.1622873.
28. Olsson T, Barcellos LF, Alfredsson L. Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. Nature Reviews Neurology 2016;13:25. doi: 10.1038/nrneurol.2016.187.
29. Hedström AK, Lima Bomfim I, Barcellos L, et al. Interaction between adolescent obesity and HLA risk genes in the etiology of multiple sclerosis. Neurology 2014;82:865-872. doi: 10.1212/WNL.0000000000000203.
30. Stampanoni Bassi M, Iezzi E, Buttari F, et al. Obesity worsens central inflammation and disability in multiple sclerosis. Multiple Sclerosis Journal;0:1352458519853473. doi: 10.1177/1352458519853473.
31. Versini M, Jeandel PY, Rosenthal E, Shoenfeld Y. Obesity in autoimmune diseases: not a passive bystander. Autoimmunity reviews 2014;13:981-1000. doi: 10.1016/j.autrev.2014.07.001.
32. Mancuso P. The role of adipokines in chronic inflammation. Immunotargets Ther 2016;5:47-56. doi: 10.2147/ITT.S73223.
33. Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. The Journal of clinical investigation 2007;117:175-184. doi: 10.1172/jci29881.
34. Elgar FJ, Stewart JM. Validity of self-report screening for overweight and obesity. Evidence from the Canadian Community Health Survey. Can J Public Health 2008;99:423-427. doi: 10.1007/bf03405254.
35. Merrill RM, Richardson JS. Validity of self-reported height, weight, and body mass index: findings from the National Health and Nutrition Examination Survey, 2001-2006. Prev Chronic Dis 2009;6:A121.
36. Nyholm M, Gullberg B, Merlo J, Lundqvist-Persson C, Råstam L, Lindblad U. The validity of obesity based on self-reported weight and height: Implications for population studies. Obesity (Silver Spring) 2007;15:197-208. doi: 10.1038/oby.2007.536.
37. Paz-Ballesteros WC, Monterrubio-Flores EA, de Jesús Flores-Rivera J, Corona-Vázquez T, Hernández-Girón C. Cigarette Smoking, Alcohol Consumption and Overweight in Multiple Sclerosis: Disability Progression. Archives of Medical Research 2017;48:113-120. doi: https://doi.org/10.1016/j.arcmed.2017.03.002.

38. Midgard R, Albrektsen G, Riise T, Kvale G, Nyland H. Prognostic factors for survival in multiple sclerosis: a longitudinal, population based study in More and Romsdal, Norway. J Neurol Neurosurg Psychiatry 1995;58:417-421.
39. Ronneberg A, Lund KE, Hafstad A. Lifetime smoking habits among Norwegian men and women born between 1890 and 1974. Int J Epidemiol 1994;23:267-276.
40. Albanes D, Jones DY, Micozzi MS, Mattson ME. Associations between smoking and body weight in the US population: analysis of NHANES II. Am J Public Health 1987;77:439-444. doi: 10.2105/ajph.77.4.439.
41. Wallin MT, Culpepper WJ, Campbell JD, et al. The prevalence of MS in the United States. A population-based estimate using health claims data 2019;92:e1029-e1040. doi: 10.1212/wnl.0000000000007035.

TABLES

Table 1 Baseline characteristics at tuberculosis screening, by later MS disease status and sex.

	Males		Females	
	Cases	**Non-cases**	**Cases**	**Non-cases**
Age 14-19				
Participants, n	228	114,822	478	109,342
Birth year (mean)	1952	1952	1952	1952
BMI <10 percentile, n(%)	19 (8)	11,507 (10)	34 (7)	11,015 (10)
BMI 10 to 84 percentile, n(%)	166 (73)	86,146 (75)	352 (74)	81,970 (75)
BMI 85 to 94 percentile, n(%)	27 (12)	11,453 (10)	51 (11)	10,920 (10)
BMI ≥ 95 percentile, n(%)	16 (7)	5,716 (5)	41 (9)	5,437 (5)
Age 20-34				
Participants, n	201	196,624	502	226,571
Birth year (mean)	1949	1942	1949	1942
BMI <10 percentile n(%)	27 (10)	21,433 (10)	50 (10)	24,491 (10)
BMI 10 to 84 percentile n(%)	193 (72)	159,405 (75)	389 (75)	179,261 (75)
BMI 85 to 94 percentile n(%)	31 (12)	21,208 (10)	48 (9)	23,411 (10)
BMI ≥ 95 percentile n(%)	16 (6)	10,419 (5)	34 (7)	11,726 (5)

Table 2 Risk (Hazard Ratio [HR]) of multiple sclerosis (MS) according to BMI category and age group at tuberculosis screening

Age category	BMI category	Cases	Non-cases	Total Risk time, y	Ajusted[1] HR, 95% CI
All	Underweight	158	83,386	3,938,465	0.87 (0.74-1.03)
	Normal	1,024	475,970	22,753,986	Ref
	Overweight	147	63,116	2,986,107	1.12 (0.94-1.33)
	Obese	80	24,887	1,150,949	**1.53** (1.22-1.92)
	Continuous[3]	1,409	647,359	30,829,506	**1.12** (1.07-1.18)
14-16[2]	Underweight	28	13,922	690,523	**0.62** (0.42-0.91)
	Normal	255	77,725	3,872,513	Ref
	Overweight	42	10,353	517,795	1.22 (0.88-1.69)
	Obese	23	3,886	191,318	**1.78** (1.16-2.73)
	Continuous	348	105,886	5,272,149	**1.19** (1.09-1.31)
17-19[2]	Underweight	49	15,506	753,136	1.07 (0.79-1.46)
	Normal	253	86,917	4,251,510	Ref
	Overweight	38	11,582	565,244	1.13 (0.80-1.59)
	Obese	18	4,273	205,702	1.43 (0.89-2.30)
	Continuous	358	118,278	5,775,592	**1.12** (1.02-1.24)
20-24[2]	Underweight	43	18,250	871,964	0.96 (0.70-1.33)
	Normal	254	105,403	5,096,810	Ref
	Overweight	38	13,810	662,665	1.22 (0.87-1.71)
	Obese	21	5,403	254,051	**1.67** (1.07-2.60)
	Continuous	356	143,222	6,885,491	**1.12** (1.02-1.24)
25-29[2]	Underweight	20	18,602	862,923	0.63 (0.40-1.00)
	Normal	184	106,751	5,024,883	Ref
	Overweight	26	13,905	644,855	1.17 (0.78-1.77)
	Obese	13	5,916	267,694	1.29 (0.73-2.26)
	Continuous	243	145,174	6,800,355	**1.12** (1.00-1.26)
30-34[2]	Underweight	18	17,106	759,918	1.33 (0.80-2.23)
	Normal	78	99,174	4,508,269	Ref
	Overweight	3	13,466	595,546	0.31 (0.10-1.00)
	Obese	5	5,409	232,185	1.21

					(0.49-3.00)
	Continuous	104	135,155	6,095,919	0.90 (0.73-1.11)

[1]Ajusted for age at screening, birth year, county and sex .[2] Underweight/normal/overweight/obese categorized as z-score: <-1/-1 to 0.99/1 to 1.99/≥2. Corresponding body mass index (kg/m2) cutpoints for age group 14-16 where <18.05/18.05-22.82/22.83-25.35/≥25.36, for age group 17-19 <19.17/19.17-24.07/24.08-26.60/≥26.61, for age group 20-24 <19.56/19.56-25.27/25.28-28.19/≥28.20, for age group 25-29 <20.14/20.14-26.13/26.14-29.12/≥29.13, for age group 30-34 <20.76/20.76-26.94/26.95-30.11/≥30.12 [3]per one unit increase in z-score

Table 3: MS risk according to BMI percentile category and age group at tuberculosis screening

Age category	BMI category	Cases	Non-cases	Ajusted[1] HR, 95% CI
All	Underweight	120	64,981	0.84 (0.70-1.02)
	Normal	1,036	485,519	Ref
	Overweight	150	64,623	1.11 (0.94-1.32)
	Obese	103	32,236	**1.53** (1.25-1.88)
Males	Underweight	38	31,255	0.91 (0.65-1.27)
	Normal	307	233,552	Ref
	Overweight	56	31,143	**1.39** (1.05-1.85)
	Obese	28	15,496	1.40 (0.95-2.06)
Females	Underweight	82	33,726	0.81 (0.65-1.02)
	Normal	729	251,967	Ref
	Overweight	94	33,480	0.99 (0.80-1.23)
	Obese	75	16,740	**1.59** (1.25-2.02)
14-16	Underweight	19	10,668	**0.54** (0.34-0.87)
	Normal	261	79,388	Ref
	Overweight	38	10,561	1.09 (0.78-1.54)
	Obese	30	5,269	**1.73** (1.19-2.53)
17-19	Underweight	34	11,854	0.97 (0.68-1-39)
	Normal	257	88,728	Ref
	Overweight	40	11,812	1.18 (0.85-1.65)
	Obese	27	5,884	**1.61** (1.08-2.39)
20-24	Underweight	35	14,349	0.99 (0.69-1.40)
	Normal	255	107,180	Ref
	Overweight	41	14,207	1.26 (0.91-1.76)
	Obese	25	7,130	**1.56** (1.04-2.36)
25-29	Underweight	15	14,578	0.58 (0.34-0.98)
	Normal	184	108,877	Ref
	Overweight	28	14,497	1.18 (0.79-1.76)
	Obese	16	7,222	1.35 (0.81-2.26)
30-34	Underweight	17	13,532	1.50 (0.89-2.53)
	Normal	79	101,346	Ref

	Overweight	3	13,546	**0.30** (0.09-0.95)
	Obese	5	6,731	1.01 (0.41-2.49)

Multiple sclerosis risk according to body mass index (BMI), age and sex-specific percentiles: <10% =underweight, ≥10% to 84% =normal weight, ≥85 to 94% = overweight, ≥95%=obese. [1]Adjusted for age at screening, sex, birth year and county. HR – Hazard ratio

Figure Legends:

Figure 1 Flowchart showing the study populations

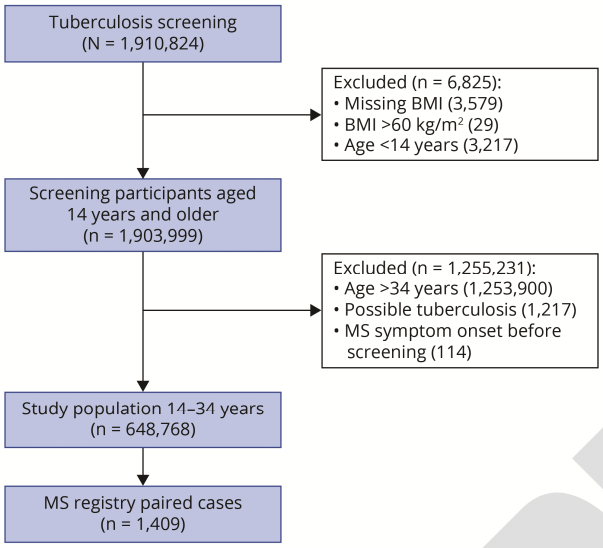


Figure 2 Hazard ratio (HR) and 95% confidence intervals (CI) for the associations between MS risk and BMI percentile category. Normal weight is reference category.

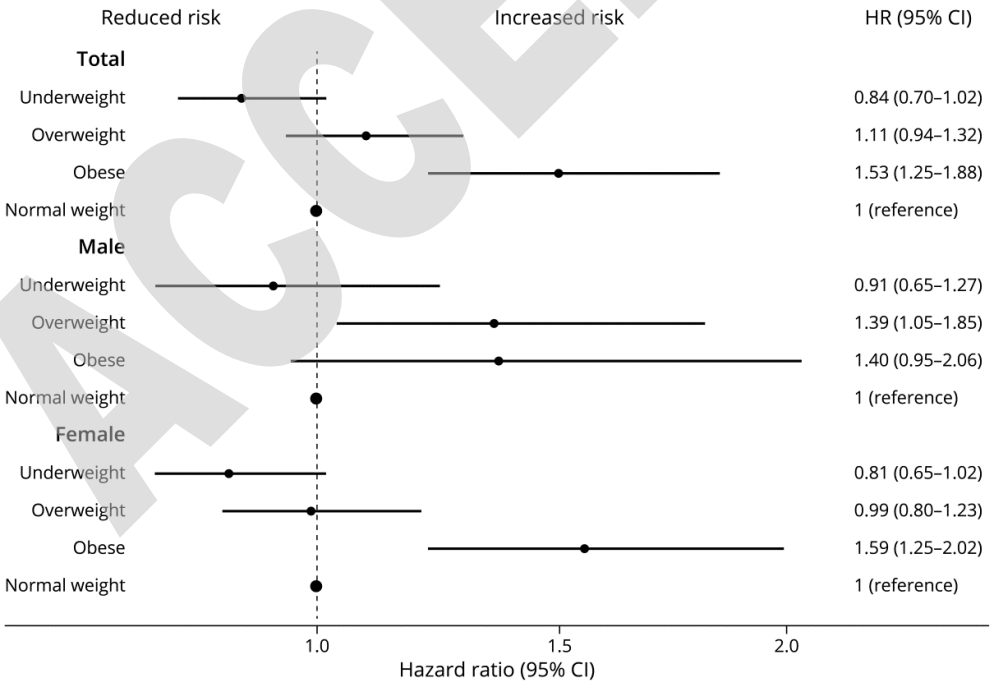
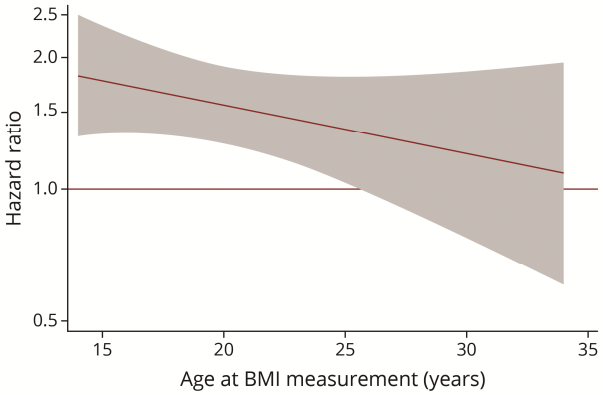


Figure 3 Hazard ratio (red line) with 95% confidence area (shaded) for multiple sclerosis according to obesity (BMI ≥95% percentile) before onset of MS.



Association of Body Mass Index in Adolescence and Young Adulthood and Long-term Risk of Multiple Sclerosis: A Population-Based Study

Rune A. Aa. Høglund, Haakon E. Meyer, Hein Stigum, et al.

Neurology published online October 25, 2021
DOI 10.1212/WNL.0000000000012957