Body size and the risk of multiple sclerosis in Norway and Italy; the EnvIMS study.

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Abstract

Background: Obesity may be a risk factor for developing multiple sclerosis (MS).

Objective: We examined if body size influences the risk of MS in a population-based case control study.

Methods: A total of 953 cases and 1717 controls from Norway and 707 cases and 1333 controls from Italy reported their body size by choosing a silhouette 1 to 9 (largest) every fifth year from age 5-30 and at time of study. The body size-related MS risk was defined by odds ratios (ORs) in logistic regression analyses adjusting for age, smoking and outdoor activity.

Results: In Norway a large body size (silhouettes 6-9) compared to silhouette 3 increased the risk of MS, especially at age 25 (OR 2.21; 95% CI 1.09-4.46 for men and OR 1.43; 95% CI 0.90-2.27 for women). When comparing silhouette 9 to1 we found a

significant dose-response from age 10 until age 30 peaking at age 25 (sex-adjusted OR 2.83; 95% CI 1.68-4.78). The association was present for at least 15 years prior to disease onset. No significant associations were found in Italy.

Conclusions: Obesity from childhood until young adulthood is a likely risk factor for MS with a seemingly stronger effect in Norway than in Italy.

Introduction

Multiple Sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system leading to disability and reduced quality of life (1, 2). The disease is believed to be the result of a complex interplay between genetic and environmental risk factors (3, 4). Serum analysis and indirect measures of vitamin D such as sun exposure and dietary intake of vitamin D provide evidence suggesting that low vitamin D levels increase the risk of MS (5, 6).

Obesity is associated with reduced circulating levels of vitamin D (7, 8). An American and a Swedish study have shown that a large body size at age 18-20 gives a twofold risk of developing MS (9, 10). Another American study found a significant increased risk for pediatric MS among obese female teenagers (11), and in addition a Danish study reported that increased BMI at age 7-13 years was associated with an increased risk of MS, especially among girls (12). Using data from a multinational case control study, we aimed to examine in Norway and Italy if a large body size prior to disease onset was associated with an age-specific or time lag-specific increased risk of MS, and if so, whether this association differed between the countries.

Methods

Study population.

The *International multicenter case-control study of Environmental Factors In Multiple Sclerosis* (EnvIMS study) is a population-based study being carried out in well-defined geographic areas in Europe (Italy, Serbia, Norway, and Sweden) and in Canada. Only MS cases with disease duration up to 10 years were invited to the study to reduce the possibility of selection and recall bias.

The data collection has been completed in Italy and in Norway. The Norwegian cases were drawn from the nationwide Norwegian MS Registry and Biobank, Haukeland University Hospital, city of Bergen(13). The Italian cases were drawn from regional MS registries in Sardinia, Ferrara and the Republic of San Marino. In each country four times as many age- and area- matched controls were selected from national population registries, and questionnaires were mailed to all eligible subjects.

The response rates to the mailings in Norway were 69.7% among cases and 36.3% among controls. In Italy including the Republic of San Marino the response rates were lower with 41.8% among cases and 20.8% among controls. Thus, a total of 1660 cases (707 from Italy and 953 from Norway) and 3050 controls (1333 from Italy and 1717 from Norway) were included. Among the cases, 533 (32.1%) were men and 1127 (67.9%) women providing a female to male ratio of 2:1 as reported in other general MS populations (14).

The questionnaire.

A detailed description of the study design and methodology is found elsewhere (15). The data were collected between 2009 and 2011 using a 6-page self-administered postal questionnaire (EnviMS-Q) which was previously tested for feasibility, acceptability and reliability (15). The questionnaire was developed to assess age-specific exposures to different environmental and life style factors such as sun-exposure, infections, smoking, body size and vitamin D intake through diet and supplements.

Body size.

The participants were asked to describe their perceived body size at ages 5, 10, 15, 20, 25, 30 years and at the time of study participation (i.e. current age) by choosing one of Stunkard's standard body silhouettes which are coded 1 to 9 where 9 represents the largest body size (16) (Figure 1). This figure rating scale (FRS) has been widely used in epidemiological research (17, 18), including a previous study on body size and the risk of MS among American female nurses (9). It has been shown to correlate well with Body Mass Index (BMI) (19). In our study we also obtained self-reported weight and height at time of study and used this to estimate current body mass index (BMI) as a means of examining the validity of the selected current body silhouette. The mean BMI for each body silhouette from our study is shown in

Figure 1.

The participants also reported their smoking history (smoke/never smoked, age at first smoke, years of smoking) and outdoor activity during summer at corresponding ages as reported body silhouettes. The latter was used as a marker for sun exposure. The

frequency of outdoor activity was reported on a four point scale (1= not that often, 2=reasonably often, 3= quite often and 4= virtually all the time).

Statistical methods.

Controls were assigned an index age based on the distribution of age at onset for the cases and randomly distributed to the controls taking into account current age. Reported body size after the age at onset/ index age was not considered as exposure. Logistic regression was used to evaluate the association between body size as a categorical variable and the risk of MS and odds ratios (ORs) are reported. Due to small sample sizes for the larger silhouettes a “large body size” category was created which combined the silhouettes 6-9. Body silhouette 3 was chosen as the reference group, because the mean BMI for this silhouette was within normal weight range according to the World Health Organization (WHO) definitions (20) allowing us to compare our results with a previous study on the same topic using the same FRS and categories (9). We stratified for sex and adjusted for age group (18-39 years, 40-49 years, 50-59 years, above 60 years at the time of the study), sun exposure (outdoor activity during summer) and smoking (smokers, ex-smokers or non-smokers at the same age as the reported body size).

We then performed logistic regression analysis including body size as a continuous variable. Using the chi-square goodness-of-fit deviance test we examined the difference between the models using body size as a categorical and continuous variable. The model with body size as a categorical variable did not show a significantly better fit (chi square with 13-6=7 d.f < 14.07 for all age groups in

both countries), suggesting a dose-response relationship. Further, we found no statistically significant interaction between sex and body size, and we therefore adjusted for sex in these analyses as well as for age group, smoking and sun exposure.
We estimated the OR for each one unit increase in body size and raised this value to the power of 8 in order to present the OR for body size 9 (largest) compared to body size 1 (smallest).

We also examined whether the association between a large body size and the risk of MS was limited to a certain time lag before the first experienced MS symptoms. We categorized the 15 years immediately prior to disease onset into 5 groups with each group covering a 3 year interval in order to ensure sufficient numbers in each group (i.e. 13-15 years prior to onset, 10-12 years, 7-9 years, 4-6 years, 1-3 years before onset). The individuals were placed in their respective group based on subtraction between age of onset/index age and age of reporting their body size. For instance, if the index age was 31 a reported body size at age 25 and at 20 represented 6 years and 11 years before onset, respectively. In the logistic regression model we used body size as a continuous variable and compared body size 9 to body size 1 following the same method as mentioned above. These analyses were adjusted for age and sex.

Finally we used the same logistic regression model to examine if the body sizes also differed between cases and controls after onset of disease. Our material included cases with a maximum disease duration of 10 years (some cases had 11 years due to some delay between inclusion and return of questionnaires). Reports of body size at current age or at other ages if the disease

onset (or index age among controls) was at age 30 or younger gave us information about the change in body size from 0-11 years after disease onset. The disease duration were divided into 4 subgroups (0-2 years, 3-5 years, 6-8 years, 9-11 years) to ensure adequate numbers of participants in each group before calculations were made.

Odds ratios (OR) were reported with 95% confidential intervals (CI) and p-values < 0.05 were considered statistically significant. The analyses were done using the statistical software SPSS version 18-20.

Ethical considerations and approvals.

The cases and controls received identical formats of the EnviMS-Q together with a cover letter with information about the study, the instructions for participation and the investigator's contact information. The participants were de-identified using a numerical code, and return of the questionnaire was considered as implied consent.

The EnviMS study received ethics approval in each research area in Italy (Sassari, Olbia-Tempio, Nuoro, Cagliari and Province of Ferrara Ethics Committee) and Norway (n. 11, 18.12.2008; NORWAY, Regional Committee for Medical and Health Research Ethics for Western Norway).

Results

The mean BMI based on self reported height and weight for each body silhouette for men and women is shown in Figure 1. The smaller body silhouettes corresponded to a slightly higher mean BMI among men than women, which may reflect some differences in the visual appearance of the male and female version of the FRS or could simply be due to different body build for the same BMI value. The Spearman´s rank correlation for ordinal variables and the Pearson´s correlation for a linear relationship between body size and BMI yielded similar results, suggesting no marked deviation from an interval scale of the body size. The analysis showed the Spearman´s rho = 0.81 and the Pearson´s r = 0.79 for Norwegian participants, and the Spearman´s rho= 0.78 and the Pearson´s = 0.79 for Italian participants. There was no significant difference in the correlation coefficient between cases and controls.

Using body size as a categorical variable and body silhouette 3 as the reference group for men and women separately, we found that the risk of MS increased with larger body size in Norway with a significant trend from age 15 until age 25. No clear trend was found in Italy (supplementary tables 1-6). The highest risk in Norway was found at age 25 where the estimated OR for a “large body size” (body silhouettes 6-9) was 2.10 (95% CI 1.08- 4.09) for men and 1.48 (95% CI 0.94- 2.32) for women (Table 1). Adjusting for smoking and outdoor activity yielded similar results. Interestingly, the individuals reporting the two smallest body sizes in all age groups from 5 years until 25 years in Norway and 5 to 20 years in Italy had a reduced risk (OR less than one) of MS compared to body size 3 .

As we found no significant interaction between sex and body size at any age (data not shown), we combined men and women when using body size as a continuous variable. Adjusting for sex, age, smoking and outdoor activity during summer we found a significantly increased risk of MS associated with increasing body sizes from age 10 to age 30 in Norway (Figure 2). The peak was at age 25 with an OR of 2.83 (95% CI 1.68- 4.78) for body size 9 compared to body size 1. In Italy a moderately and non-significantly increased risk was seen up to age 20, while no increased risk was seen for age 25 and a slightly decreased risk was seen for age 30. One should note that since there might be a deviation from an interval scale of body sizes, one should interpret these estimates with caution.

We also assessed the effect of body size on the risk of MS in relation to the number of years before MS onset using body size as a continuous variable in the logistic regression analysis. In Norway the risk for body size 9 compared to body size 1 was increased during at least 15 years before the first symptoms with peaks at 7-9 years (OR= 4.72, 95% CI 2.19- 10.21) and at 1-3 years before disease onset (OR = 3.63, 95% CI 1.41-9.33) (Figure 3). In Italy the same analyses showed no such pattern.

After the onset of MS the pattern changed with smaller body sizes among the cases relative to controls, being significantly different at 6-8 years after onset in both countries.

Discussion

We found that a large body size during adolescence and young adulthood was associated with an increased risk of MS in Norway with the strongest effect at around 25 years of age. In Italy we observed a similar, but statistically non-significant pattern. In Norwegians the risk of MS related to a large body size was increased in at least 15 years prior to MS onset, indicating a possible accumulating effect of large body size on the development of MS.

Our results are consistent with previous studies that have reported an increased risk of MS among overweight and obese persons (9-12). Analyses of American women in the Nurses' Health Study I and II showed a twofold increased risk for MS later in life among those who were obese (defined by BMI) at age 18 and among those who had a large body size (defined by Stunkard's FRS) at age 20 (9). In a Swedish population BMI > 27 at age 20 doubled the risk of MS in both men and in women (10), and in an American population obese girls, but not boys, aged 11-18 years had a 78% increased risk of developing pediatric MS (onset <18 years) (11). A recent Danish prospective cohort study also discovered a stronger effect of obesity on the risk of MS among girls than among boys aged 7-13 years (14).

In our study we were able to show that being overweight at all age periods from early childhood until 30 years of age increases the risk of MS in Norway. Further, while previous studies have found an effect primarily for individuals who are obese, we found in our study a dose-response relationship over the whole scale.

The apparent relationship between a large body size and the risk of MS may be due to different mechanisms. Low vitamin D levels are associated with increased risk of MS (5, 6). Obese teenagers (21, 22) and adults (8) have decreased levels of circulating vitamin D which can be explained by trapping of the hydrophobic vitamin D in fatty tissue (23). Thus a constant suboptimal levels of circulating vitamin D may contribute to the increased risk of developing MS.

Obesity also leads to a chronic inflammatory state mediated by the adipose tissue (24) possibly induced by CD8+ cells (25) which are shown to play an important role in MS-inflammation (26). Further, higher serum-levels of pro-inflammatory cytokines (interleukin-6 and tumor necrosis factor-alfa) have been found in obese subjects indicating not only local, but also systemic inflammation in obesity (27). A constant over-activity of the immune system due to adipositas may lead to an autoimmune cascade influencing the disease development in MS. This idea is supported by a recent finding of a significant interaction between the MS risk gene HLA-DRB1*15 allele and BMI $\geq$ 27 suggesting that the HLA-related antigen presentation in adipose tissue leads to CNS directed autoimmunity in MS susceptible individuals (28).

On the other hand, low vitamin D itself may also contribute to the inflammation seen in obese individuals as vitamin D has been shown to have immunomodulatory actions (29-31) with a beneficial effect of high vitamin D levels. Added to this complexity, a large Norwegian prospective cohort study has reported that low circulating 25(OH) vitamin D increased the incidence of obesity later in life (32), saying that low vitamin D may be one of the causal factors of obesity. Therefore, obesity can either be a confounder for low vitamin D status *or* contribute to the risk of MS through other mechanisms than those mediated through the actions of vitamin D.

Nevertheless, these observations are less likely to explain the seemingly protective effect of being in the thin end of Stunkard's FRS compared to the more "normal" body size 3 as one would think that the risk among the normal and thin persons would be similar if the association between weight and MS-risk largely was due to obesity-related inflammation.

In our analyses we adjusted for outdoor activity during the relevant periods as a mediator for sun exposure. The ultraviolet radiation from sun light both stimulates the production of vitamin D in the skin and suppresses immune responses relevant to MS independent of vitamin D (33). The adjustment did not change the estimates noticeably. This suggests that our findings are not simply reflecting overweight children being less outdoors and thereby having lower levels of vitamin D, and also argue against confounding by other immunomodulatory effects of ultraviolet radiation.

Our study is the first to investigate the association between body size and the risk of MS in a southern European population. We did not find any clear associations in the Italian data. It is difficult to interpret the divergent results in the two countries, but it might be related to differences in the genetic profile or dietary habits. Still, a similar trend of inverse association between obesity and vitamin D levels are seen in Italy as in Norway (34, 35).

Our study has several strengths, but also some limitations. One of them is the low response rates among controls. For this reason we cannot rule out the possibility of selection bias having some impact on our results. The mean BMI is significantly lower among both cases and controls in Italy compared to Norway (data not shown) indicating a generally "thinner" study population in Italy.

Another limitation of our study relates to the subjective self-reporting of body size at various ages and height and weight at the time of study participation. However, the participants were encouraged to ask their parents or other near relatives in case of hesitation when answering the EnvIMS-Q. Further, we found no significant difference in the correlation of BMI and body size between cases and controls at study time. This argues against a difference in self-perception of body size in relation to disease status and also a difference in recall.

In summary, we have shown that a large body size from childhood to adulthood is associated with MS in Norway, but less so in Italy. This might relate to low circulating vitamin D or a chronic inflammatory state in obese individuals.

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Conflicts of interest statement

AM. Landtblom has received speakers honorary and grants from Biogen Idec, Teva, Bayer, Merck, Serono. A. Lossius has received speaker honoraria and unrestricted research grants from Novartis. KM. Myhr has received speaker honoraria, travel support and/or unrestricted research grants from Bayer Schering, Biogen Idec, Genzyme, Sanofi Aventis, Novartis, and Merck Serono. T. Holmøy has received speaker honoraria, travel support and unrestricted research grants from Sanofi Aventis, Biogen Idec, Bayer Schering, Novartis, and Merck Serono. K. Bjørnevik, I. Casetta, J. Drulovic, E. Granieri, M.T. Kampman, K. Lauer, S. Magalhaes, T. Pekmezovic, M. Pugliatti, T. Riise, K. Wesnes, C. Wolfson have no conflicts of interest in relation to the publication topic.

References

1. Wynia K, Middel B, van Dijk JP, De Keyser JH, Reijneveld SA. The impact of disabilities on quality of life in people with multiple sclerosis. Mult Scler. 2008;14(7):972-80.

2. Nortvedt MW, Riise T, Myhr KM, Nyland HI. Quality of life in multiple sclerosis: measuring the disease effects more broadly. Neurology. 1999;53(5):1098-103.

3. Handel AE, Giovannoni G, Ebers GC, Ramagopalan SV. Environmental factors and their timing in adult-onset multiple sclerosis. Nature reviews Neurology. 2010;6(3):156-66.

4. Lin R, Charlesworth J, van der Mei I, Taylor BV. The genetics of multiple sclerosis. Practical neurology. 2012;12(5):279-88.

5. Ascherio A, Munger KL, Simon KC. Vitamin D and multiple sclerosis. Lancet Neurol. 2010;9(6):599-612.

6. Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. JAMA. 2006;296(23):2832-8.

7. Goldner WS, Stoner JA, Thompson J, Taylor K, Larson L, Erickson J, et al. Prevalence of vitamin D insufficiency and deficiency in morbidly obese patients: a comparison with non-obese controls. Obes Surg. 2008;18(2):145-50.

8. Konradsen S, Ag H, Lindberg F, Hexeberg S, Jorde R. Serum 1,25-dihydroxy vitamin D is inversely associated with body mass index. European journal of nutrition. 2008;47(2):87-91.

9. Munger KL, Chitnis T, Ascherio A. Body size and risk of MS in two cohorts of US women. Neurology. 2009;73(19):1543-50.

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. Mult Scler. 2012.

11. Langer-Gould A, Brara SM, Beaber BE, Koebnick C. Childhood obesity and risk of pediatric multiple sclerosis and clinically isolated syndrome. Neurology. 2013.

12. Munger KL, Bentzen J, Laursen B, Stenager E, Koch-Henriksen N, Sorensen TI, et al. Childhood body mass index and multiple sclerosis risk: a long-term cohort study. Mult Scler. 2013.

13. Myhr KM, Grytten N, Aarseth JH. The Norwegian Multiple Sclerosis Registry and Biobank. Acta neurologica Scandinavica Supplementum. 2012(195):20-3.

14. Alonso A, Hernan MA. Temporal trends in the incidence of multiple sclerosis: a systematic review. Neurology. 2008;71(2):129-35.

15. Pugliatti M, Casetta I, Drulovic J, Granieri E, Holmoy T, Kampman MT, et al. A questionnaire for multinational case-control studies of environmental risk factors in multiple sclerosis (EnvIMS-Q). Acta neurologica Scandinavica Supplementum. 2012(195):43-50.

16. Stunkard AJ, Sorensen T, Schulsinger F. Use of the Danish Adoption Register for the study of obesity and thinness. Research publications - Association for Research in Nervous and Mental Disease. 1983;60:115-20.

17. Sorbara M, Geliebter A. Body image disturbance in obese outpatients before and after weight loss in relation to race, gender, binge eating, and age of onset of obesity. The International journal of eating disorders. 2002;31(4):416-23.

18. Lewis DM, Cachelin FM. Body image, body dissatisfaction, and eating attitudes in midlife and elderly women. Eating disorders. 2001;9(1):29-39.

19. Bulik CM, Wade TD, Heath AC, Martin NG, Stunkard AJ, Eaves LJ. Relating body mass index to figural stimuli: population-based normative data for Caucasians. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity. 2001;25(10):1517-24.

20. WHO. WHO global database on Body Mass Index [Database]. 2012. Available from: http://www.who.int/gho/ncd/risk_factors/bmi_text/en/.

21. Kremer R, Campbell PP, Reinhardt T, Gilsanz V. Vitamin D status and its relationship to body fat, final height, and peak bone mass in young women. J Clin Endocrinol Metab. 2009;94(1):67-73.

22. Gordon CM, DePeter KC, Feldman HA, Grace E, Emans SJ. Prevalence of vitamin D deficiency among healthy adolescents. Archives of pediatrics & adolescent medicine. 2004;158(6):531-7.

23. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. The American journal of clinical nutrition. 2000;72(3):690-3.

24. Aleksandrova K, Nimptsch K, Pischon T. Influence of Obesity and Related Metabolic Alterations on Colorectal Cancer Risk. Current nutrition reports. 2013;2(1):1-9.

25. Nishimura S, Manabe I, Nagasaki M, Eto K, Yamashita H, Ohsugi M, et al. CD8+ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. Nature medicine. 2009;15(8):914-20.

26. Kasper LH, Shoemaker J. Multiple sclerosis immunology: The healthy immune system vs the MS immune system. Neurology. 2010;74 Suppl 1:S2-8.

27. Gobel RJ, Jensen SM, Frokiaer H, Molgaard C, Michaelsen KF. Obesity, inflammation and metabolic syndrome in Danish adolescents. Acta paediatrica. 2012;101(2):192-200.

28. Hedstrom AK, Lima Bomfim I, Barcellos L, Gianfrancesco M, Schaefer C, Kockum I, et al. Interaction between adolescent obesity and HLA risk genes in the etiology of multiple sclerosis. Neurology. 2014;82(10):865-72.

29. Correale J, Ysrraelit MC, Gaitan MI. Vitamin D-mediated immune regulation in multiple sclerosis. J Neurol Sci. 2011;311(1-2):23-31.

30. Deluca HF, Cantorna MT. Vitamin D: its role and uses in immunology. FASEB J. 2001;15(14):2579-85.

31. Koch MW, Metz LM, Agrawal SM, Yong VW. Environmental factors and their regulation of immunity in multiple sclerosis. J Neurol Sci. 2013;324(1-2):10-6.

32. Mai XM, Chen Y, Camargo CA, Jr., Langhammer A. Cross-Sectional and Prospective Cohort Study of Serum 25-Hydroxyvitamin D Level and Obesity in Adults: The HUNT Study. Am J Epidemiol. 2012;175(10):1029-36.

33. Becklund BR, Severson KS, Vang SV, DeLuca HF. UV radiation suppresses experimental autoimmune encephalomyelitis independent of vitamin D production. Proceedings of the National Academy of Sciences of the United States of America. 2010;107(14):6418-23.

34. Adami S, Bertoldo F, Braga V, Fracassi E, Gatti D, Gandolini G, et al. 25-hydroxy vitamin D levels in healthy premenopausal women: association with bone turnover markers and bone mineral density. Bone. 2009;45(3):423-6.

35. Pacifico L, Anania C, Osborn JF, Ferraro F, Bonci E, Olivero E, et al. Low 25(OH)D3 levels are associated with total adiposity, metabolic syndrome, and hypertension in Caucasian children and adolescents. European journal of endocrinology / European Federation of Endocrine Societies. 2011;165(4):603-11.

Table 1. The risk of MS compared to body size 3 at age 25 in Norway.

	Men 25 years			Women 25 years		
Body size	**Controls/ cases (N(%))**	**OR[a] (95% CI)**	**OR[b] (95% CI)**	**Controls/ cases (N(%))**	**OR[a] (95% CI)**	**OR[b] (95% CI)**
1	38 (10%)/15 (6%)	0.72 (0.37-1.40)	0.69 (0.34-1.38)	79 (8%)/33 (6%)	0.87 (0.55-1.37)	0.88 (0.55-1.41)
2	87 (22%)/42 (17%)	0.86 (0.54-1.38)	0.83 (0.51-1.36)	244 (23%)/102 (19%)	0.87 (0.64-1.18)	0.87 (0.63-1.19)
3	123 (31%)/70 (28%)	1 (ref)	1 (ref)	300 (29%)/146 (27%)	1 (ref)	1 (ref)
4	82 (21%)/70 (28%)	1.47 (0.95-2.28)	1.54 (0.98-2.44)	236 (23%)/131 (24%)	1.12 (0.84-1.51)	1.17 (0.86-1.58)
5	48 (12%)/28 (11%)	0.99 (0.57-1.73)	0.95 (0.53-1.68)	132 (13%)/85 (16%)	1.28 (0.91-1.79)	1.34 (0.95-1.90)
6-9	20 (5%)/25 (10%)	2.10 (1.08-4.09)	2.21 (1.09-4.46)	55 (5%)/43 (8%)	1.48 (0.94-2.32)	1.43 (0.90-2.27)
Total	398 (100%)/250 (100%)			1046 (100%)/540 (100%)		
P-trend		0,01	0,005		0,004	0,004

N: Numbers; OR: odds ratios; CI: Confidential intervals; [a]Odds ratios adjusted for age groups; [b] Odds ratios adjusted for age-group, smoking and sunexposure

SUPPLEMENTAL TABLES

Table 1. The risk of MS compared to body size 3 at age 5 in Norway and Italy.

NORWAY	**Men 5 years**			**Women 5 years**		
Body Size	**Controls/ cases (N(%))**	**OR (95% CI)**	**OR*(95% CI)**	**Controls/ cases (N(%))**	**OR (95% CI)**	**OR*(95% CI)**
1	188 (42%)/ 94 (36%)	0.61 (0.38-0.98)	0.61 (0.38-0.97)	425(35%)/ 198 (31%)	0.85 (0.64-1.14)	0.89 (0.67-1.19)
2	115 (26%)/ 69 (26%)	0.73 (0.45-1.19)	0.74 (0.45-1.22)	306 (25%)/ 165 (26%)	0.95 (0.71-1.28)	1.00 (0.74-1.36)
3	56 (13%)/ 46 (18%)	1 (ref)	1 (ref)	200 (16%)/ 114 (18%)	1 (ref)	1 (ref)
4	31 (7%)/ 26 (10%)	1.03 (0.53-1.98)	1.05 (0.55-2.04)	156 (13%)/ 90 (14%)	1.04 (0.73-1.47)	1.07 (0.76-1.53)
5	29 (7%)/ 17 (7%)	0.72 (0.35-1.47)	0.71 (0.35-1.46)	83 (7%)/ 45 (7%)	0.99 (0.64-1.52)	1.00 (0.64-1.54)
6-9	25 (6%)/ 9 (3%)	0.43 (0.18-1.02)	0.46 (0.20-1.10)	43 (4%)/ 29 (5%)	1.24 (0.73-2.11)	1.26 (0.74-2.15)
Total	444 (100%)/ 261 (100%)			1213 (100%)/641 (100%)		
P-trend		0.48	0.32		0.09	0.11

ITALY	**Men 5 years**			**Women 5 years**		
Body Size	**Controls/ cases (N(%))**	**OR (95% CI)**	**OR*(95% CI)**	**Controls/ cases (N(%))**	**OR (95% CI)**	**OR*(95% CI)**

1	170 (45%)/ 96 (42%)	0.82 (0.49-1.40)	0.80 (0.47-1.38)	377 (49%)/ 159 (42%)	0.74 (0.50-1.09)	0.76 (0.51-1.13)
2	84 (22%)/ 54 (23%)	0.93 (0.52-1.65)	0.93 (0.52-1.67)	153 (20%)/ 96 (25%)	1.08 (0.71-1.66)	1.11 (0.72-1.71)
3	46 (12%)/ 31 (13%)	1 (ref)	1 (ref)	90 (12%)/ 52 (14%)	1 (ref)	1 (ref)
4	32 (9%)/ 20 (9%)	0.94 (0.45-1.93)	0.94 (0.45-1.98)	70 (9%)/ 39 (10%)	0.96 (0.57-1.61)	0.97 (0.57-1.65)
5	24 (6%)/ 16 (7%)	0.97 (0.44-2.11)	0.84 (0.37-1.90)	52 (7%)/ 21 (6%)	0.70 (0.38-1.29)	0.76 (0.41-1.41)
6-9	19 (5%)/ 14 (6%)	1.05 (0.46-2.42)	1.02 (0.44-2.37)	25 (3%)/ 10 (3%)	0.68 (0.30-1.54)	0.67 (0.30-1.51)
Total	375 (100%)/ 231 (100%)			767 (100%)/ 377 (100%)		
P-trend		0.40	0.49		0.62	0.69

N: Numbers; OR: odds ratios; CI: Confidential intervals; [a]Odds ratios adjusted for age groups; [b] Odds ratios adjusted for age-group and sunexposure

Table 2. The risk of MS compared to body size 3 at age 10 in Norway and Italy.

NORWAY	**Men 10 years**			**Women 10 years**		
Body Size	**Controls/ cases (N(%))**	**OR (95% CI)**	**OR*(95% CI)**	**Controls/ cases (N(%))**	**OR (95% CI)**	**OR*(95% CI)**
1	153 (34%)/ 67 (25%)	0.60 (0.37-0.97)	0.59 (0.36-0.96)	350 (29%)/ 158 (25%)	0.85 (0.63-1.15)	0.87 (0.64-1.18)
2	141 (32%)/ 96 (36%)	0.92 (0.58-1.47)	0.89 (0.55-1.41)	360 (30%)/ 184 (29%)	0.93 (0.69-1.24)	0.94 (0.70-1.26)
3	62 (14%)/ 46 (17%)	1 (ref)	1 (ref)	206 (17%)/ 115 (18%)	1 (ref)	1 (ref)
4	41 (9%)/ 25 (9%)	0.82 (0.44-1.54)	0.88 (0.47-1.67)	166 (14%)/ 111 (17%)	1.23 (0.88-1.72)	1.25 (0.89-1.75)
5	22 (5%)/ 18 (7%)	1.12 (0.54-2.33)	1.11 (0.53-2.32)	87 (7%)/ 50 (8%)	1.04 (0.68-1.58)	0.99 (0.65-1.51)
6--9	25 (6%)/ 12 (5%)	0.66 (0.30-1.45)	0.71 (0.32-1.60)	46 (4%)/ 25(4%)	1.03 (0.60-1.76)	1.08 (0.62-1.86)
Total	444 (100%)/ 264(100%)			1215 (100%)/ 643 (100%)		
P-trend		0.2	0.11		0.05	0.07

ITALY	**Men 10 years**			**Women 10 years**		
Body Size	**Controls/ cases (N(%))**	**OR (95% CI)**	**OR*(95% CI)**	**Controls/ cases (N(%))**	**OR (95% CI)**	**OR*(95% CI)**
1	114 (30%)/ 65 (28%)	0.63 (0.37-1.06)	0.63 (0.37-1.07)	311 (40%)/ 137 (36%)	0.70 (0.48-1.02)	0.71 (0.49-1.05)%

2	128 (34%)/ 65 (28%)	0.56 (0.34-0.94)	0.58 (0.34-0.98)	195 (25%)/ 100 (26%)	0.81 (0.54-1.20)	0.79 (0.53-1.19)
3	48 (13%)/ 42 (18%)	1 (ref)	1 (ref)	100 (13%)/ 64 (17%)	1 (ref)	1 (ref)
4	49 (13%)/ 31 (14%)	0.72 (0.39-1.34)	0.72 (0.39-1.35)	81 (10%)/ 41 (11%)	0.80 (0.49-1.30)	0.77 (0.47-1.26)
5	15 (4%)/ 17 (7%)	1.25 (0.55-2.81)	1.19 (0.52-2.70)	60 (8%)/ 20 (5%)	0.52 (0.29-0.94)	0.54 (0.30-0.99)
6--9	22 (6%)/ 9 (4%)	0.46 (0.19-1.11)	0.47 (0.20-1.15)	29 (4%)/ 18 (5%)	0.96 (0.49-1.86)	0.93 (0.48-1.82)
Total	376 (100%)/ 229 (100%)			776(100%)/ 380 (100%)		
P-trend		0.32	0.36		0.67	0.77

N: Numbers; OR: odds ratios; CI: Confidential intervals; [a]Odds ratios adjusted for age groups; [b] Odds ratios adjusted for age-group and sunexposure

Table 3. The risk of MS compared to body size 3 at age 15 in Norway and Italy.

NORWAY	Men 15 years			Women 15 years		
Body Size	**Controls/ cases (N(%))**	**OR[a] (95% CI)**	**OR[b] (95% CI)**	**Controls/ cases (N(%))**	**OR[a] (95% CI)**	**OR[b] (95% CI)**
1	102 (23%)/ 38 (14%)	0.48 (0.30-0.78)	0.47 (0.29-0.78)	240 (20%)/ 99 (15%)	0.76 (0.56-1.04)	0.77 (0.56-1.06)
2	158 (36%)/ 87 (33%)	0.71 (0.47-1.07)	0.67 (0.44-1.02	331 (27%)/ 171 (27%)	0.92 (0.70-1.21)	0.92 (0.70-1.22)
3	91 (20%)/ 71 (26%)	1 (ref)	1 (ref)	281 (23%)/ 157 (24%)	1 (ref)	1 (ref)
4	50 (11%)/ 40 (15%)	1.03 (0.61-1.72)	1.04 (0.61-1.78)	227 (19%)/ 127 (20%)	1.00 (0.74-1.34)	0.98 (0.73-1.33)
5	25 (6%)/ 16 (6%)	0.83 (0.41-1.67)	0.76 (0.36-1.60)	96 (8%)/ 63 (10%)	1.20 (0.82-1.74)	1.16 (0.79-1.71)
6-9	16 (4%)/ 15 (6%)	1.22 (0.56-2.64)	1.13 (0.51-2.53)	34 (3%)/ 25 (4%)	1.31 (0.75-2.29)	1.28 (0.72-2.26)
Total	442 (100%)/ 267 (100%)			1209 (100%)/ 642 (100%)		
P-trend		0.003	0.004		0.01	0.023

ITALY	Men 15 years			Women 15 years		
Body Size	**Controls/ cases (N(%))**	**OR[a] (95% CI)**	**OR[b] (95% CI)**	**Controls/ cases (N(%))**	**OR[a] (95% CI)**	**OR[b] (95% CI)**
1	62 (17%)/ 37 (17%)	0.73 (0.42-1.25)	0.80 (0.45-1.43)	180 (23%)/ 86 (23%)	0.77 (0.54-1.11)	0.75 (0.51-1.09)

2	132 (36%)/ 67 (30%)	0.65 (0.42-1.02)	0.67 (0.42-1.08)	240 (31%)/ 91 (24%)	0.61 (0.43-0.86)	0.57 (0.39-0.81)
3	78 (21%)/ 60 (27%)	1 (ref)		157 (20%)/ 98 (26%)	1 (ref)	
4	51 (14%)/ 32 (14%)	0.80 (0.46-1.40)	0.84 (0.47-1.51)	102 (13%)/ 57 (15%)	0.89 (0.59-1.34)	0.94 (0.62-1.44)
5	24 (7%)/ 19 (9%)	1.05 (0.52-2.10)	1.06 (0.50-2.25)	71 (9%)/ 30 (8%)	0.66 (0.40-1.09)	0.69 (0.42-1.14)
6-9	17 (5%)/ 8 (4%)	0.61 (0.25-1.52)	0.71 (0.28-1.83)	29 (4%)/ 17 (4%)	0.91 (0.47-1.75)	0.99 (0.51-1.95)
Total	364 (100%)/ 223 (100%)			779 (100%)/ 379 (100%)		
P-trend		0.39	0.59		0.37	0.13

N: Numbers; OR: odds ratios; CI: Confidential intervals; [a]Odds ratios adjusted for age groups; [b] Odds ratios adjusted for age-group, smoking and sunexposure

Table 4. The risk of MS compared to body size 3 at age 20 in Norway and Italy.

NORWAY	Men 20 years			Women 20 years		
Body Size	**Controls/ cases (N(%))**	**OR[a] (95% CI)**	**OR[b] (95% CI)**	**Controls/ cases (N(%))**	**OR[a] (95% CI)**	**OR[b] (95% CI)**
1	56 (13%)/ 21 (8%)	0.51 (0.28-0.91)	0.52 (0.28-0.94)	149 (13%)/60 (10%)	0.76 (0.54-1.09)	0.73 (0.51-1.05)
2	140 (32%)/61 (23%)	0.58 (0.38-0.89)	0.57 (0.37-0.88)	291 (25%)/145 (23%)	0.92 (0.70-1.21)	0.88 (0.67-1.16)
3	107 (25%)/79 (30%)	1 (ref)	1 (ref)	323 (28%)/177 (29%)	1 (ref)	1 (ref)
4	79 (18%)/59 (23%)	1.0 (0.64-1.57)	1.02 (0.64-1.62)	253 (22%)/121 (20%)	0.87 (0.66-1.16)	0.87 (0.66-1.16)
5	35 (8%)/26 (10%)	1.02 (0.56-1.82)	1.01 (0.55-1.87)	104 (9%)/83 (13%)	1.43 (1.01-2.01)	1.41 (1.0-1.98)
6-9	14 (3%)/16 (6%)	1.58 (0.72-3.45)	1.48 (0.69-3.22)	50 (4%)/32 (5%)	1.11 (0.68-1.79)	1.01 (0.63-1.63)
Total	431 (100%)/262 (100%)			1170 (100%)/618 (100%)		
P-trend		0.0005	0.001		0.03	0.02

ITALY	Men 20 years			Women 20 years		
Body Size	**Controls/ cases (N(%))**	**OR[a] (95% CI)**	**OR[b] (95% CI)**	**Controls/ cases (N(%))**	**OR[a] (95% CI)**	**OR[b] (95% CI)**
1	33 (10%)/ 23 (11%)	0.92 (0.49-1.74)	0.91 (0.46-1.78)	114 (16%)/ 43 (12%)	0.69 (0.45-1.07)	0.74 (0.47-1.17)

2	87 (26%)/ 48 (23%)	0.80 (0.50-1.29)	0.78 (0.47-1.29)	234 (32%)/ 105 (30%)	0.82 (0.59-1.16)	0.83 (0.58-1.19)
3	93 (28%)/ 67 (32%)	1 (ref)	1 (ref)	177 (24%)/ 97 (28%)	1 (ref)	1 (ref)
4	79 (24%)/ 51 (24%)	0.89 (0.56-1.43)	0.98 (0.60- 1.62)	131 (18%)/ 65 (19%)	0.90 (0.61-1.33)	0.95 (0.63-1.43)
5	25 (8%)/ 13 (6%)	0.71 (0.34-1.51)	0.96 (0.44-2.11)	46 (6%)/ 24 (7%)	0.95 (0.54-1.65)	0.96 (0.53-1.73)
6-9	13 (4%)/ 9 (4%)	0.98 (0.39-2.43)	0.88 (0.34-2.30)	21 (3%)/ 14 (4%)	1.19 (0.58-2.45)	1.30 (0.60-2.83)
Total	330 (100%)/ 211 (100%)			723 (100%)/ 348 (100%)		
P-trend		0.97	0.61		0.12	0.13

N: Numbers; OR: odds ratios; CI: Confidential intervals; [a]Odds ratios adjusted for age groups; [b]Odds ratios adjusted for age-group, smoking and sun exposure

Table 5. The risk of MS compared to body size 3 at age 25 in Norway and Italy.

NORWAY	**Men 25 years**			**Women 25 years**		
Body Size	**Controls/ cases (N(%))**	**OR[a] (95% CI)**	**OR[b] (95% CI)**	**Controls/ cases (N(%))**	**OR[a] (95% CI)**	**OR[b] (95% CI)**
1	38 (10%)/15 (6%)	0.72 (0.37-1.40)	0.69 (0.34-1.38)	79 (8%)/33 (6%)	0.87 (0.55-1.37)	0.88 (0.55-1.41)
2	87 (22%)/42 (17%)	0.86 (0.54-1.38)	0.83 (0.51-1.36)	244 (23%)/102 (19%)	0.87 (0.64-1.18)	0.87 (0.63-1.19)
3	123 (31%)/70 (28%)	1 (ref)	1 (ref)	300 (29%)/146 (27%)	1 (ref)	1 (ref)
4	82 (21%)/70 (28%)	1.47 (0.95-2.28)	1.54 (0.98-2.44)	236 (23%)/131 (24%)	1.12 (0.84-1.51)	1.17 (0.86-1.58)
5	48 (12%)/28 (11%)	0.99 (0.57-1.73)	0.95 (0.53-1.68)	132 (13%)/85 (16%)	1.28 (0.91-1.79)	1.34 (0.95-1.90)
6-9	20 (5%)/25 (10%)	2.10 (1.08-4.09)	2.21 (1.09-4.46)	55 (5%)/43 (8%)	1.48 (0.94-2.32)	1.43 (0.90-2.27)
Total	398 (100%)/250 (100%)			1046 (100%)/540 (100%)		
P-trend		0.01	0.005		0.004	0.004

ITALY	**Men 25 years**			**Women 25 years**		
Body Size	Controls/ cases (N(%))	OR[a] (95% CI)	OR[b] (95% CI)	Controls/ cases (N(%))	OR[a] (95% CI)	OR[b] (95% CI)
1	12 (5%)/ 8 (5%)	0.84 (0.32-2.25)	0.87 (0.30-2.52)	59 (10%)/ 24 (8%)	0.88 (0.51-1.51)	0.98 (0.56-1.73)

2	54 (21%)/ 38 (23%)	1.01 (0.58-1.75)	1.01 (0.56-1.82)	182 (30%)/ 89 (31%)	1.07 (0.75-1.54)	1.12 (0.77-1.64)
3	77 (29%)/ 51 (31%)	1 (ref)	1 (ref)	189 (32%)/ 87 (30%)	1 (ref)	1 (ref)
4	70 (27%)/ 40 (24%)	0.82 (0.48-1.39)	0.84 (0.48-1.49)	108 (18%)/ 55 (19%)	1.10 (0.73-1.66)	1.17 (0.76-1.81)
5	38 (14%)/ 21 (13%	0.82 (0.43-1.56)	1.08 (0.54-2.17)	42 (7%)/ 23 (8%)	1.19 (0.67-2.10	1.17 (0.65-2.11)
6-9	12 (5%)/ 9 (5%)	1.04 (0.40-2.68)	1.08 (0.37-3.12)	19 (3%)/ 9 (3%)	1.02 (0.44-2.35)	1.00 (0.41-2.44)
Total	263 (100%)/ 167 (100%)			599 (100%)/ 287 (100%)		
P-trend		0.65	0.95		0.58	0.77

N: Numbers; OR: odds ratios; CI: Confidential intervals; [a]Odds ratios adjusted for age groups; [b]Odds ratios adjusted for age-group, smoking and sun exposure

NORWAY	Men 30 years	Women 30 years

Table 6. The risk of MS compared to body size 3 at age 30 in Norway and Italy.

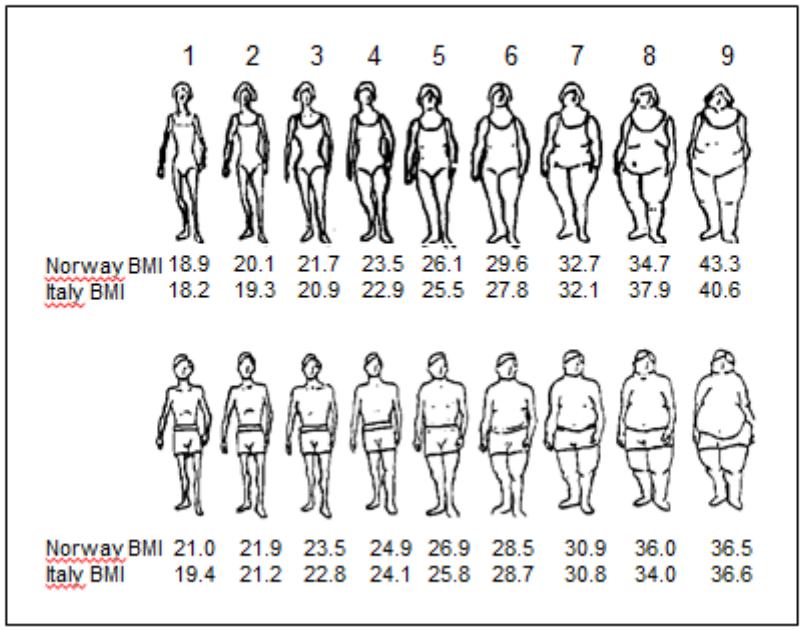
Body Size	Controls/ cases (N(%))	OR (95% CI)	OR*(95% CI)	Controls/ cases (N(%))	OR (95% CI)	OR*(95% CI)
1	19 (6%)/ 9 (4%)	0.89 (0.37-2.12)	0.96 (0.38-2.42)	43 (5%)/ 17 (4%)	0.80 (0.44-1.47)	0.70 (0.37-1.31)
2	55 (16%)/ 36 (17%)	1.22 (0.70-2.13)	1.00 (0.56-1.80)	139 (16%)/ 69 (15%)	0.99 (0.69-1.43)	0.93 (0.63-1.36)
3	86 (25%)/ 45 (21%)	1 (ref)	1 (ref)	232 (26%)/ 120 (26%)	1 (ref)	1 (ref)
4	103 (30%)/ 63 (29%)	1.14 (0.70-1.85)	1.23 (0.74-2.06)	242 (28%)/ 125 (27%)	0.97 (0.71-1.32)	0.96 (0.69-1.32)
5	53 (15%)/ 32 (15%)	1.12 (0.63-1.98)	1.13 (0.62-2.07)	150 (17%)/ 73 (16%)	0.90 (0.63-1.29)	0.91 (0.63-1.32)
6-9	29 (8%)/ 30 (14%)	1.96 (1.04-3.68)	1.96 (1.00-3.79)	72 (8%)/ 54 (12%)	1.35 (0.89-2.06)	1.28 (0.83-1.98)
Total	345 (100%)/ 215 (100%)			878 (100%)/ 458 (100%)		
P-trend		0.16	0.08		0.35	0.24

ITALY	**Men 30 years**			**Women 30 years**		
Body Size	**Controls/ cases (N(%))**	**OR (95% CI)**	**OR*(95% CI)**	**Controls/ cases (N(%))**	**OR (95% CI)**	**OR*(95% CI)**
1	6 (3%)/ 3 (2%)	0.61 (0.14-2.70)	0.82 (0.17-4.0)	35 (8%)/ 8 (4%)	0.59 (0.26-1.36)	0.57 (0.23-1.37)
2	14 (7%)/ 23 (18%)	2.67 (1.21-5.88)	2.79 (1.21-6.46)	91 (21%)/ 60 (29%)	1.74 (1.12-2.71)	1.70 (1.07-2.70)
3	60 (30%)/ 36 (29%)	1 (ref)	1 (ref)	159 (36%)/ 60 (29%)	1 (ref)	1 (ref)
4	50 (25%)/ 32 (25%)	1.02 (0.55-1.89)	1.19 (0.61-2.32)	100 (23%)/ 48 (23%)	1.25 (0.79-1.98)	1.21 (0.75-1.97)
5	48 (24%)/ 26 (21%)	0.88 (0.47-1.67)	0.94 (0.47-1.85)	40 (9%)/ 26 (13%)	1.72 (0.97-3.07)	1.65 (0.91-3.01

6--9	20 (10%)/ 6 (5%)	0.49 (0.18-1.37)	0.59 (0.19-1.83)	17 (4%)/ 5 (2%)	0.78 (0.27-2.21)	0.68 (0.21-2.17)
Total	198 (100%)/ 126 (100%)			442 (100%)/ 207 (100%)		
P-trend		0.03	0.05		0.75	0.84

N: Numbers; OR: odds ratios; CI: Confidential intervals; [a]Odds ratios adjusted for age groups; [b]Odds ratios adjusted for age-group, smoking and sun exposure

Figure 1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Italy BMI 18.2 19.3 20.9 22.9 25.5 27.8 32.1 37.9 40.6
Norway BMI 21.0 21.9 23.5 24.9 26.9 28.5 30.9 36.0 36.5
Italy BMI 19.4 21.2 22.8 24.1 25.8 28.7 30.8 34.0 36.6