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Childhood body mass index and multiple sclerosis risk: a long-term cohort study

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Abstract

Background—Obesity in late adolescence has been associated with an increased risk of multiple sclerosis (MS); however, it is not known if body size in childhood is associated with MS risk.

Methods—Using a prospective design we examined whether body mass index (BMI) at ages 7–13 was associated with MS risk among 303,998 individuals in the Copenhagen School Health Records Register (CSHRR). Linking the CSHRR with the Danish MS registry yielded 774 MS cases (501 girls, 273 boys). We used Cox proportional hazards models, to estimate the hazard ratios (HR) and 95% confidence intervals.

Results—Among girls, at each age 7–13, a 1-unit increase in BMI z-score was associated with an increased risk of MS (HR_{age 7}=1.20, 95%CI: 1.10–1.30; HR_{age 13}=1.18, 95%CI: 1.08–1.28). Girls who were 95th percentile for BMI had a 1.61–1.95-fold increased risk of MS as compared to girls <85th percentile. The associations were attenuated in boys. The pooled HR for a 1-unit increase in BMI z-score was at age 7 was 1.17, 95%CI: 1.09–1.26, and at age 13, 1.15, 95%CI: 1.07–1.24.

Conclusion—Having a high BMI in early life is a risk factor for MS, but the mechanisms underlying the association remain to be elucidated.

Keywords

Multiple Sclerosis; Cohort studies; Risk factors in epidemiology; Obesity

Introduction

The growing world-wide obesity epidemic has multiple deleterious effects on public health, including cardiovascular and metabolic diseases, but recently, obesity has also been associated with an increased risk of multiple sclerosis (MS), a demyelinating disease of the central nervous system. In a prospective study of over 200,000 US women, being obese in late adolescence/early adulthood (age 18) was associated with a 2-fold increased risk of MS,¹ and being overweight during this time period with a 40% increased risk of MS. A recent Swedish case-control study also reported a 2-fold increased risk of MS among individuals who were obese at age 20, and found that the association was similar in men and women.² These findings lead to the question of whether there is an association between body size in childhood or early adolescence and MS risk, and if this association is similar in girls and boys. Therefore, we conducted a prospective, longitudinal study in a population of Danish schoolchildren to determine whether body mass index in late childhood/early adolescence predicted their risk of developing MS later in life and whether this risk differed between girls and boys.

Methods

Study population

The Copenhagen School Health Records Register (CSHRR) is an ongoing cohort of children born since 1930 who attended public or private primary (elementary) school in Copenhagen.³ Until 1984, every year between the ages of 7 and 13 inclusive, weight and height of the children were measured and recorded, as previously described.⁴ Thereafter, the children were measured at primary school entry and often at exit only. This study was based on 351,742 children born between 1930 and 1983. Children born after 1983 were not eligible for this study because we expected too few cases of MS based on their young age. On April 2, 1968, Denmark began issuing personal identification numbers to all living residents of Denmark. Children were excluded from this study if they did not have a personal identification number, were diagnosed with MS before April 2, 1968, died or emigrated before 1968, if they left the CSHRR cohort before age 14 (the minimum age for inclusion in this study), or if they were missing BMI measurements at all ages, leaving 302,043 children for this study. (Figure 1) Body mass index (BMI) in kg/m² was calculated at each age for each child using the weight and height measurements. Birth weight was reported by the parents and recorded in the children's health records for those children born in 1936 or later (n=203,809).

Standard Protocol Approvals, Registrations, and Patient Consents

The current study did not involve any contacts to patients and was, as requested for register-based research, approved by the Danish Data Protection Agency and the human subjects committee of the Harvard School of Public Health.

Identification of MS cases in the CSHRR

The Danish MS Registry (DMSR) began as a nationwide prevalence study of MS in 1949 and was officially established in 1956.⁵ All neurology departments in Denmark, as well as

the two MS rehabilitation clinics, the Danish MS Treatment Register, and the National Patient Register notify the DMSR of individuals with an MS diagnosis, which is then confirmed by a DMSR neurologist. Cases occurring prior to 1994 were confirmed using the diagnostic criteria of Allison and Millar⁶ and those in 1994-2004 by the diagnostic criteria of Poser.⁷ The DMSR is estimated to capture over 90% of the MS cases occurring in Denmark, and the diagnostic validity using autopsied cases as reference is 94%.⁸ Individuals in the CSHRR were linked with the DMSR via the personal identification number. This linkage yielded 774 MS cases that occurred between April 2, 1968 (the date the personal identification numbers were issued) and December 31, 2004, among individuals with at least one weight and height measurement in the CSHRR.

Statistical analysis

Differences in mean BMI between MS cases and non-cases were tested with a t-test. BMI was modeled in two ways: 1) as a continuous z score variable, and 2) as a categorical variable comparing large body size to smaller body sizes based on the age- and sex-specific percentile distribution. Z scores were created using an internal reference population of children with weight and height data between 1955 and 1960 as there was a low and stable prevalence of overweight/obesity during this time.⁴ In *a priori* categorizations, within each age and sex-specific group, BMI was categorized as <85th percentile, 85th-<95th, 95th. These categories were chosen to evaluate whether the extremes of body size (i.e. the body sizes 85th percentile are likely to correspond to overweight/obesity) among these children were associated with MS risk.

Hazard ratios of MS associated with BMI were estimated using Cox proportional hazards models, using age as the time scale and stratification by birth cohorts (1930-1935, 1936-1939, 1940-1945, 1946-1952, 1953-1973, and 1974-1983) defined by important historical periods in Danish history (e.g. World War II and reconstruction) that may affect BMI to account for secular trends in BMI.³ Follow-up began at age 14 or April 2, 1968 (date the personal identification number was issued), whichever was later, and ended at date of MS onset, date of death, date of emigration, date of loss to follow-up, or December 31, 2004, whichever was earlier. Analyses were done separately in girls and boys, and heterogeneity between the sex-specific estimates was assessed using a test of the Schoenfeld residuals. We pooled the results of girls and boys together by using the variable "sex" as a stratification variable in the Cox proportional hazards models. Tests of proportional hazards did not reveal any violations of the assumption. P values <0.05 were considered statistically significant. The statistical programs STATA and SAS were used for the calculations.

Results

Of the 774 MS cases occurring among CSHRR participants during follow-up, 501 were among girls and 273 were among boys. As expected, BMI increased with increasing age in both girls and boys. (Table 1) At each age 7 through 13 inclusive, girls and boys who later developed MS had a higher BMI than girls and boys who did not develop MS. The differences between cases and non-cases were only significant among the girls (Table 1).

Among *girls*, at each age from 7 to 13, a 1-unit increase in a BMI z-score was associated with significant hazard ratios of MS of 1.17 to 1.21 (Table 2). As compared with girls with BMI <85th percentile, those in the 95th percentile had a significant 1.61 to 1.95-fold increased risk of MS at every age (Table 3), while among those with a BMI between the 85th-<95th percentiles a significant increased risk of MS was seen only at ages 12 and 13.

Among *boys*, there was a significant hazard ratio of 1.14 to 1.15 for MS with every 1-unit increase in BMI z-score at ages 8 through 10, but no significant associations at other ages (Table 2). Boys with a BMI 95th percentile at age 7 had a significant 1.81-fold increased risk of MS as compared with boys with BMI <85th percentile, and while there was a tendency to an increased risk at other ages, none of the associations attained significance (Table 3).

While overall the associations between the age-specific BMI measures and risk of MS were attenuated in the boys as compared to the girls, there was no statistical evidence for heterogeneity between the sex- and age-specific hazard ratios (p value for heterogeneity ranged from 0.29-0.81 for the BMI z score analysis, and 0.27-0.94 for BMI in the 95th percentile versus <85th percentile). We therefore combined the girls and boys in one analysis. Overall, there was a significant 1.15-1.18-fold increased risk of MS per a 1-unit increase in the BMI z-score in girls and boys combined (Figure 2), and a significant 1.56-1.81-fold increased risk of MS among children in with BMI 95th percentile as compared to those with BMI <85th percentile. (Table 3)

Birth weight was not associated with risk of MS in either girls or boys. In pooled analyses of both girls and boys, using birth weight of 2.751-3.25 kg as the reference, $HR_{2.0-2.75\text{ kg}}=0.94$, 95% CI: 0.72-1.24; $HR_{>3.25-3.75}=1.06$, 0.87-1.29; $HR_{>3.75-4.25}=1.19$, 0.94-1.51; $HR_{>4.25}=0.96$, 0.63-1.45.

All of the above analyses were stratified by birth cohort to account for secular changes in body size. There were no consistent trends or differences over time in the associations between body size and MS risk in either boys or girls (data not shown), either within or between the birth cohorts.

Discussion

In this large, prospective study among Danish school children, higher BMI during childhood and early adolescence was associated with an increased risk of MS. Among boys, the association was weaker than for girls, and overall not significant; however, this may be at least in part a result of the smaller sample size and thus lower power. Heterogeneity tests comparing the effect estimates of boys and girls suggest they were not materially different, and justified pooling of the estimates, though we cannot rule out true biological differences. Additionally, we found no association between birth weight and risk of MS, which is in agreement with other studies.^{9, 10}

The results of this study add to the previous findings in the US and Sweden of a 40% increased risk of MS among individuals who were overweight, and a 2-fold increased risk among those who were obese (BMI ≥ 30 kg/m²) at age 18¹ or 20,² by suggesting that

overweight or obesity in childhood and early adolescence is also associated with an increased risk of MS. There are several strengths of the current study including the population-based prospective design, large sample size, and, importantly, objective measurements of height and weight during early life. Further, while the CSHRR only includes children who attended public or private school in the city of Copenhagen, the Danish MS Registry is a nationwide registry and would capture cases of MS occurring in adulthood in the CSHRR cohort throughout the country. Thus, we are capturing cases irrespective of whether they have been already in the medical system due to potential complications of overweight/obesity, which otherwise could create a serious selection bias.

Our results are consistent with BMI in childhood being etiologically important for MS in adulthood, and interestingly, there was essentially no variation in the risk of MS associated with BMI across ages 7 to 13, suggesting that, at least among girls, a high pre-puberty BMI (e.g. at age 7) and high pubertal BMI (e.g. at ages 11 to 13) have the same association with MS risk. One consideration, however, is that body size is correlated over the life course and in the two Nurses' Health Study (NHS) cohorts, the correlation between body size, as self-reported by selecting a best representative pictogram, at age 10 and 20 was 0.59 (NHS II) and 0.87 (NHS I).¹ The positive association observed between having a larger body size at age 5 or 10 and MS risk in the NHS did not persist after adjusting for body size at age 20; however, the high correlations between age-specific BMI values may prevent adequate separation of effects with the statistical methods used in that study.¹¹ One important consideration is that weight and body size over the life course, while correlated, is a more dynamic process that typically thought and obese/overweight children do not necessarily become obese/overweight adults.¹² Thus, the increased risk of MS observed with having a larger body size at each age 7 through 13 may be of biological importance irrespective of the tracking through adult life, and certainly they suggest that prevention of or intervention on childhood overweight or obesity may contribute to reduce MS risk.

Information on other MS risk factors such as infection with Epstein-Barr virus (EBV),¹³ HLA-DRB1 genotype,¹⁴ and vitamin D nutritional status,¹⁵ is not available in the CSHRR, and potential confounding by these factors cannot be evaluated. However, seropositivity to EBV was similar in obese and normal weight individuals¹⁶ and studies of HLA-DRB1 genotype have not addressed a potential association with body size. Vitamin D may be on the causal pathway between body size and MS risk (see below), in which case, adjusting for vitamin D status may not be appropriate.

Why having a large body size in childhood would increase the risk of MS in adulthood is not known, but there are a few possibilities to consider. Blood levels of 25-hydroxyvitamin D (25(OH)D), the main circulating vitamin D metabolite and nutritional biomarker of vitamin D status,¹⁷ are generally lower (~15 ng/mL or less difference) in overweight/obese adults as compared to those of normal weight,^{18, 19} and high BMI has also been associated with lower 25(OH)D in children (4-13 years old).^{20, 21} In a prospective study among US military personnel, elevated 25(OH)D levels during young adulthood in non-Hispanic whites were associated with a decreased risk of MS.²² Thus, if being overweight or obese during early life is causally related to MS, it may be acting through the vitamin D pathway. Another possible pathway is based on the increased secretion of adipokines from the adipose tissue in

obesity. There is evidence that some adipokines, such as leptin, can modulate immune system function, including reducing the proliferation of regulatory T-cells,²³ and promoting an inflammatory T helper 1 cell response.²⁴ Additionally, leptin-deficient mice are protected against experimental autoimmune encephalomyelitis,²⁵ an animal model of MS, and administration of leptin worsens the disease.²⁵ High leptin levels have also been associated with lower regulatory T-cells in MS patients.²⁶

Overweight/obesity is a major public health problem worldwide and trends of increasing body size among children are particularly concerning. This study expands on previous work, suggesting that having a high BMI in early life is a risk factor for MS. The incidence of MS has been increasing in Denmark, particularly among women²⁷, and our study suggests that a parallel increase in overweight/obesity in the Danish population²⁸ may, in part, explain this. Participants in the CSHRR are predominately of European descent,³ and these findings may not be generalizable to other race/ethnic groups. Confirmation of these findings in other populations, studies of body size over the full course of childhood and adolescence, and exploration of possible pathways are needed.

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Figure 1.

Figure 2.

Table 1
Mean BMI (kg/m²) for the total cohort and MS cases, by sex and age

Age (yrs)	Girls				Boys			
	Cohort		MS cases		Cohort		MS cases	
	N	BMI (SD)	Weight equivalent to a 1-unit increase in BMI z-score (kg)	P value	N	BMI (SD)	Weight equivalent to a 1-unit increase in BMI z-score (kg)	P value
7	139915	15.5 (1.4)	2.2	0.001	143606	15.6 (1.3)	2	0.21
8	142014	15.8 (1.5)	2.6	0.001	145738	15.8 (1.3)	2.4	0.08
9	138748	16.2 (1.7)	3.2	0.001	141726	16.2 (1.5)	2.9	0.07
10	135975	16.7 (1.9)	3.8	0.005	138434	16.6 (1.7)	3.5	0.06
11	135149	17.2 (2.1)	4.6	0.001	137401	17.1 (1.9)	4.2	0.10
12	133971	17.8 (2.3)	5.4	0.001	135857	17.5 (2.0)	4.8	0.22
13	132227	18.6 (2.4)	6.2	0.002	133409	18.1 (2.2)	5.5	0.20

Table 2
Hazard ratio^a of MS associated with a 1-unit increase in BMI z-score, by sex and age among children in the CSHRR

Age (yrs)	Girls		Boys	
	Cases/person-years	HR (95% CI)	Cases/person-years	HR (95% CI)
7	482/4,181,649	1.20 (1.10-1.30) ^b	256/4,219,714	1.12 (0.99-1.28)
8	484/4,254,596	1.19 (1.09-1.30) ^b	261/4,291,291	1.14 (1.01-1.30)
9	485/4,217,682	1.19 (1.09-1.30) ^b	258/4,240,624	1.14 (1.01-1.30)
10	476/4,184,745	1.17 (1.07-1.28) ^c	264/4,195,501	1.15 (1.01-1.30)
11	475/4,174,946	1.21 (1.10-1.32) ^b	262/4,178,638	1.12 (0.99-1.27)
12	478/4,151,554	1.20 (1.10-1.30) ^b	260/4,144,003	1.11 (0.98-1.26)
13	475/4,114,170	1.18 (1.08-1.28) ^b	252/4,084,469	1.10 (0.97-1.25)

^a Stratified by birth cohort (1930-1935, 1936-1939, 1940-1945, 1946-1952, 1953-1973, and 1974-1983)

^b p<0.0001

^c p<0.01

Table 3
HR^c and 95% CI of MS associated with BMI percentile, by sex and age among children in the CSHRR

Age (yrs)	All			Girls			Boys		
	<85%ile	85-<95%ile	95%ile	<85%ile	85-<95%ile	95%ile	<85%ile	85-<95%ile	95%ile
7									
n/p-y	605/7,208,856	77/811,331	56/381,176	396/3,585,064	50/405,048	36/191,536	209/3,623,792	27/406,283	20/189,640
HR	1.0	1.12	1.70 ^d	1.0	1.11	1.65 ^c	1.0	1.13	1.81 ^b
95% CI	(ref)	(0.88-1.42)	(1.30-2.24)	(ref)	(0.83-1.49)	(1.17-2.32)	(ref)	(0.76-1.68)	(1.14-2.86)
8									
n/p-y	611/7,317,753	81/835,642	53/392,492	397/3,641,266	51/416,607	36/196,723	214/3,676,487	30/419,035	17/195,769
HR	1.0	1.14	1.56 ^c	1.0	1.10	1.61 ^c	1.0	1.20	1.46
95% CI	(ref)	(0.90-1.43)	(1.18-2.07)	(ref)	(0.83-1.48)	(1.15-2.27)	(ref)	(0.82-1.75)	(0.89-2.94)
9									
n/p-y	607/7,238,855	76/830,824	60/388,628	395/3,608,317	47/414,096	43/195,269	212/3,630,538	29/416,728	17/193,359
HR	1.0	1.07	1.78 ^e	1.0	1.03	1.95 ^e	1.0	1.15	1.45
95% CI	(ref)	(0.85-1.36)	(1.36-2.32)	(ref)	(0.76-1.39)	(1.42-2.67)	(ref)	(0.78-1.70)	(0.89-2.38)
10									
n/p-y	604/7,170,894	82/825,217	54/384,135	389/3,579,745	48/412,363	39/192,637	215/3,591,149	34/412,854	15/191,498
HR	1.0	1.17	1.62 ^d	1.0	1.05	1.78 ^d	1.0	1.38	1.31
95% CI	(ref)	(0.93-1.47)	(1.23-2.14)	(ref)	(0.78-1.42)	(1.28-2.47)	(ref)	(0.96-1.98)	(0.78-2.21)
11									
n/p-y	598/7,148,222	79/822,736	60/382,625	381/3,569,851	52/412,621	42/192,473	217/3,578,371	27/410,115	18/190,152
HR	1.0	1.13	1.81 ^e	1.0	1.16	1.95 ^e	1.0	1.08	1.56
95% CI	(ref)	(0.90-1.43)	(1.39-2.37)	(ref)	(0.87-1.55)	(1.42-2.68)	(ref)	(0.73-1.61)	(0.96-2.52)
12									
n/p-y	590/7,097,639	96/815,404	52/382,514	374/3,550,407	68/409,507	36/191,641	216/3,547,232	28/405,897	16/190,873
HR	1.0	1.41 ^c	1.60 ^c	1.0	1.57 ^d	1.72 ^c	1.0	1.12	1.37
95% CI	(ref)	(1.14-1.75)	(1.20-2.12)	(ref)	(1.22-2.04)	(1.23-2.43)	(ref)	(0.76-1.67)	(0.83-2.28)
13									
n/p-y	583/7,012,473	93/807,550	51/378,618	377/3,517,191	62/406,135	36/190,845	206/3,495,282	31/401,415	15/187,773

Age (yrs)	All			Girls			Boys		
	<85%ile	85-<95%ile	95%ile	<85%ile	85-<95%ile	95%ile	<85%ile	85-<95%ile	95%ile
HR	1.0	1.38 ^c	1.58 ^c	1.0	1.44 ^c	1.72 ^c	1.0	1.27	1.32
95% CI	(ref)	(1.11-1.71)	(1.19-2.10)	(ref)	(1.10-1.88)	(1.22-2.42)	(ref)	(0.87-1.85)	(0.78-2.22)

^aStratified by birth cohort (1930-1935, 1936-1939, 1940-1945, 1946-1952, 1953-1973, and 1974-1983);

^b p<0.05;

^c p<0.01;

^d p<0.001;

^e p<0.0001