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ORIGINAL ARTICLE

Obesity during childhood and adolescence increases susceptibility to multiple sclerosis after accounting for established genetic and environmental risk factors

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Summary
Objective: To investigate the association between obesity and multiple sclerosis (MS) while accounting for established genetic and environmental risk factors.
Methods: Participants included members of Kaiser Permanente Medical Care Plan, Northern California Region (KPNC) (1235 MS cases and 697 controls). Logistic regression models were used to estimate odds ratios (ORs) with 95% confidence intervals (95% CI). Body mass index (BMI) or body size was the primary predictor of each model. Both incident and prevalent MS cases were studied.

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Results: In analyses stratified by gender, being overweight at ages 10 and 20 were associated with MS in females ($p < 0.01$). Estimates trended in the same direction for males, but were not significant. BMI in 20s demonstrated a linear relationship with MS (p-trend = 9.60×10^{-4}), and a twofold risk of MS for females with a BMI $\geq 30\,kg/m^2$ was observed (OR = 2.15, 95% CI 1.18, 3.92). Significant associations between BMI in 20s and MS in males were not observed. Multivariate modelling demonstrated that significant associations between BMI or body size with MS in females persisted after adjusting for history of infectious mononucleosis and genetic risk factors, including *HLA-DRB1*15:01* and established non-HLA risk alleles.
Interpretation: Results show that childhood and adolescence obesity confer increased risk of MS in females beyond established heritable and environmental risk factors. Strong evidence for a dose-effect of BMI in 20s and MS was observed. The magnitude of BMI association with MS is as large as other known MS risk factors.

Introduction

Multiple sclerosis (MS) is a severe and complex disease of the central nervous system (CNS) that affects over 400,000 Americans and 2.5 million people worldwide [1]. It remains the second leading cause of neurological disability in young to middle-aged adults [2]. While advances in clinical management have been made over the past 30 years, long-term prognosis for most individuals diagnosed with MS remains poor [3]. After 20 years from onset, more than 60% of individuals with MS require ambulatory assistance; very progressive MS occurs in approximately 5—10% of individuals [2,4]. Strong evidence supports the contribution of both genetic and environmental factors to disease susceptibility as demonstrated by increased, though incomplete, disease concordance amongst monozygotic twins (~25%) compared to dizygotic twins (~5%) [5—7]. Substantial progress has been made towards the identification of several MS risk factors including the *HLA-DRB1*15:01* allele within the major histocompatibility complex (MHC) and other non-HLA genetic variants [8—10], as well as exposure to tobacco smoke, Epstein—Barr Virus (EBV) infection, and lower levels of vitamin D [11—13]; however, the mechanisms underlying disease pathogenesis are still undefined.

Recently, obesity has emerged as an important risk factor for MS. Association between body mass at age 18 [14] or age 20 [15] and MS onset later in life was observed in two studies, where obese participants demonstrated greater than a twofold increase in risk of MS compared to those at normal weight. Additionally, childhood obesity and risk of both paediatric [16] and later onset [17] MS were reported. In paediatric cases, an increased risk was more prominent amongst females, and extremely obese children had over three times the odds of developing disease compared to normal weight children [16]. In a Danish study, childhood obesity was associated with 1.75 increased risk of developing MS later in life when comparing BMI of girls $\geq$ 95th percentile to girls < 85th percentile [17]. While obesity has been shown convincingly to be associated with MS, previous studies have not investigated this relationship while accounting for effects of other established risk factors. As both childhood and adolescence may be critical exposure periods for MS [18], this study aimed to examine whether body size/mass during childhood and adolescence were associated with MS while controlling for a number of environmental and genetic risk factors, including history of infectious mononucleosis and *HLA-DRB1*15:01* status, the strongest genetic contributor to MS [19].

Methods

Participants

Data were collected from members of Kaiser Permanente Medical Care Plan, Northern California Region (KPNC). Both incident and prevalent MS cases were studied. KPNC is an integrated health services delivery system with a membership of 3.2 million that comprises about 25—30% of the population of a 22 county service area and is the largest healthcare provider in northern California. Comparisons with the general population have shown that the membership is objectively representative; however, persons in impoverished neighbourhoods are underrepresented [20]. The membership is stable