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Original Article

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Estimated and projected burden of multiple sclerosis attributable to smoking and childhood and adolescent high body-mass index: a comparative risk assessment

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Abstract

Background: Smoking and childhood and adolescent high body-mass index (BMI) are leading lifestyle-related risk factors of global premature morbidity and mortality, and have been associated with an increased risk of developing multiple sclerosis (MS). This study aims to estimate and project the proportion of MS incidence that could be prevented with elimination of these risk factors.

Methods: Prevalence estimates of high BMI during childhood/adolescence and smoking in early adulthood, and relative risks of MS, were obtained from published literature. A time-lag of 10 years was assumed between smoking in early adulthood and MS incidence, and a time-lag of 20 years was assumed between childhood/adolescent high BMI and MS incidence. The MS population attributable fractions (PAFs) of smoking and high BMI were estimated as individual and combined risk factors, by age, country and sex in 2015, 2025 and 2035 where feasible.

Results: The combined estimated PAFs for smoking and high BMI in 2015 were 14, 11, 12 and 12% for the UK, USA, Russia and Australia in a conservative estimate, and 21, 20, 19 and 16% in an independent estimate, respectively. Estimates for smoking are declining over time, whereas estimates for high early life BMI are rising. The PAF for high early life BMI is highest in the USA and is estimated to increase to 14% by 2035.

Conclusions: Assuming causality, there is the potential to substantially reduce MS incidence with the elimination of lifestyle-related modifiable risk factors, which are the target of global public health prevention strategies.

Key words: Multiple sclerosis, smoking, obesity, population attributable fraction, risk factor

Key Messages

- The population attributable fraction of incident MS cases in the UK resulting from combined effects of smoking and high body mass index (BMI) in childhood/adolescence is 21 and 14% in independent and conservative estimates respectively.
- The population attributable fraction of incident MS cases related to high BMI is anticipated to increase most markedly in the USA over the next 20 years from 11 to 14% attributable risk.
- Assuming causality, a substantial proportion of MS incidence could be reduced by addressing lifestyle-related modifiable risk factors, which are currently the target of global public health prevention strategies.

Background

Temporal trends in multiple sclerosis (MS) indicate increasing incidence and prevalence.[1,2] Environmental risk factors, including smoking and childhood high body-mass index (BMI)[3,4] appear to contribute to MS development alongside genetic risk. Previous studies have estimated that 53.3% of MS risk is directly attributable to non-genetic factors,[5] and that up to one in five MS cases could be attributable to smoking.[6] Smoking and high BMI are leading global drivers of many non-communicable diseases and cause significant premature morbidity and mortality.[7]

Bradford–Hill criteria demonstrate strong evidence indicating a causal relationship between smoking and subsequent MS development.[8] Although the relationship between early life high BMI and subsequent MS risk is more complex to study epidemiologically, recent Mendelian randomization studies strongly and consistently support a causal relationship.[9,10] Countries differ in age- and sex-specific risk factor prevalence, and risk factor prevalence changes over time; in MS there is a substantial time lag between risk factor exposure and subsequent clinical disease diagnosis, leading to considerable complexity in estimating the impact of behavioural changes.

The population attributable fraction (PAF) is defined as the proportional reduction in average disease risk that would be achieved by eliminating the exposure(s), if all other disease-related factors remain constant.[11] Although this remains a mathematical concept, the PAF provides a valuable means of visualizing the impact of population-based interventions.

The aim of this study is to estimate and project the reduction in incident MS cases that could be achieved with the elimination of smoking in young adulthood and high BMI in childhood across four countries, in order to highlight the potential impact of population-level public health initiatives.

Methods

Included risk factors and countries

Smoking and high BMI were selected as risk factors for study because: (i) they are lifestyle-related risk factors, (ii) existing evidence suggests a likely causal association and (iii) robust estimates of global prevalence over time are available.[12,13]

The UK, USA, Russia and Australia were selected as countries of interest because of their size, geographical breadth and because they are majority White populations.

Sources of data

Estimates of relative risks (RR) for associations between smoking, early-life high BMI and MS were identified through a literature search in MEDLINE via PubMed. Articles were searched without time or language restrictions up to 1 May 2020, using the search terms: 'smoking' OR 'body-mass index' OR 'overweight' OR 'obesity', AND 'multiple sclerosis', AND 'attributable fraction' OR 'attributable proportion'. Country-specific RR estimates were not used, as these were not available for all countries, and, where available, the studies were of substantially smaller size. The data sources provided odds ratios rather than RRs due to the methods of data collection; given the relative rarity of MS, the odds ratio was assumed to provide a good approximation of the RR for the purposes of this study.[14]

Prevalence estimates of 'daily smokers' in early adulthood (age 20–24 years) and early life high BMI (during childhood and adolescence) were obtained from the Global Burden of Disease (GBD) and the Non-Communicable Disease Risk Factor Collaboration (NCD-RisC), respectively.[12,13] BMI prevalence estimates were categorized as 'overweight' BMI $>$ 1SD $<$ 2SD and 'obese' BMI $>$ 2SD, from age- and sex-specific means. Methods used in the GBD and NCD-RisC are described elsewhere.[12,13]

Statistical analysis

PAFs were calculated using the following formula, where p = prevalence of the risk factor in the population: PAF = p(RR−1)/p(RR−1)+1).[15] Results were aggregated across sex by weighting the sex-specific PAFs by a 3:1 female:male MS sex ratio.[16]

We assumed a 10-year lag between smoking and MS incidence, as smoking behaviours are established in early adulthood, and a 20-year lag between high childhood BMI and MS incidence.[17] Analyses were stratified by sex, and restricted to age-standardized risk factor prevalence in the age group 20–24 years for smoking, and 5–19 years for high BMI. Individuals were assumed to be exposed throughout the exposure period.

Smoking PAFs were estimated for 2015 and projected for 2025 using prevalence estimates from 2005 and 2015, respectively. PAFs for high BMI were estimated for 2015 and projected for 2025 and 2035 using prevalence estimates from 1995, 2005 and 2015, respectively. PAFs for high BMI were generated by summing the PAFs for 'overweight' and 'obesity'. PAFs were estimated individually for each risk factor and combined for both smoking and high BMI. Combined estimates were calculated in two ways: (i) assuming risk factors as independent using the formula $PAF=1-[(1-PAF_{Smoking})\times(1-PAF_{High\ BMI})]$, and (ii) assuming risk factors as fully overlapping (conservative estimate) using only the larger of each sex- and country-specific PAF for smoking/high BMI.

Sensitivity analyses

Sensitivity analyses were performed using the upper and lower bounds of the 95% uncertainty intervals in order to generate the highest and lowest estimated possible PAFs.

Results

The largest meta-analysis examining smoking behaviour prior to MS incorporated 14 573 cases and 579 812 controls.[8] This meta-analysis provided an odds ratio of MS in smokers of 1.54 [95% confidence interval (CI) 1.46–1.63] (Table 1).

The RR estimate for childhood and adolescent high BMI was selected based on a recent study with RR measures in units consistent with prevalence estimates for BMI in children and adolescence,[10] i.e. standard deviations (SDs) from age- and sex-specific means. This Mendelian randomization study provided an odds ratio associated with increased childhood BMI (defined as >1 SD from age- and sex-specific mean) of 1.24 (95% CI 1.05–1.45) (Table 1). Categorizing BMI using a BMI SD score is a standard method of assessing weight and obesity in children compared with classic BMI categorizations used in adulthood. It is thought to provide a more accurate representation of an international population than other measures.[18] This study was judged to be preferable for use than a population-based study, as truly prospective studies measuring BMI in childhood or adolescence (the putative high-risk period) are relatively small[17] or use less internationally relevant definitions of increased BMI during childhood.

Smoking attributable fraction

Approximately 10% of the population risk of MS in 2015 was attributable to smoking (10–14%; as shown in Table 1a and Figure 1a). Inter-country variation was greater for males. The PAF attributed to smoking was more than double in males compared with females in Russia (22 vs 9%), reflecting differences in smoking prevalence. The proportion of incident MS attributable to smoking is projected to decline by 2025, as shown in Table 1a and Figure 1a.

Childhood and adolescent high BMI attributable fraction

In 2015, early life high BMI was associated with a higher PAF than smoking in the USA and Australia, and an equivalent level in the UK, as shown in Table 1b and Figure 1b. Inter-country variation was similar across males and females, shown in Table 1b and Figure 1b. The PAF of high BMI is projected to rise markedly: by 2035 this study estimates that it will account for ∼14% of overall incident MS risk in the USA, as can be seen in Table 1b, Figure 1b.

Combined attributable fraction and sensitivity analyses

When treated as independent factors, the combined PAF for smoking and childhood high BMI provided an estimate of ∼20% in Australia, the UK and the USA in 2015, as illustrated in Figure 2a. In a conservative estimate, combined smoking and high BMI gave a PAF of 14% in the UK and 11% in the USA in 2015, as shown in Figure 2b. The largest PAF resulting from combined effects of smoking and high BMI was in the UK: 21 and 14% in independent and conservative estimates respectively. As can be seen in Figure 2, the combined PAF of smoking and high BMI on incident MS is anticipated to remain relatively constant between 2015 and 2025 in combined estimates, largely due to the impact of increasing prevalence of increased BMI being offset by declines in smoking. For example, the combined PAF in the USA is estimated to change from 19 to 20% between 2015 and 2025 in the

Table 1 Proportion of incident MS attributable to (a) smoking and (b) childhood and adolescent high BMI, by sex

(a)

Risk factor: smoking

Odds ratio[a]: 1.54 — 95% CI: 1.46–1.63

	Prevalence estimate (95% uncertainty interval)		Population attributable fraction (%)	
	2005	2015	2015	2025
Males				
Australia	28 (24–32)	20 (16–25)	13.1	9.7
USA	25 (24–26)	17 (16–18)	11.9	8.4
UK	31 (27–36)	29 (21–38)	14.3	13.5
Russia	51 (47–57)	44 (36–53)	21.6	19.2
Females				
Australia	23 (20–26)	17 (13–22)	11.0	8.4
USA	19 (19–20)	13 (12–14)	9.3	6.6
UK	29 (24–33)	24 (18–32)	13.5	11.5
Russia	19 (15–24)	18 (10–27)	9.3	8.9

(b)

Risk factor: high BMI in childhood and adolescence

Odds ratio (overweight and obese)[b]: 1.24 — 95% CI: 1.05–1.45

		Prevalence estimate (95% uncertainty interval)			High BMI, population attributable fraction (%)		
		1995	2005	2015	2015	2025	2035
Males							
Australia	1SD<BMI<2SD	19 (14–25)	21 (16–26)	22 (16–29)	8.6	10.6	11.7
	BMI>2SD	8 (5–13)	11 (7–16)	13 (8–19)			
USA	1SD<BMI<2SD	18 (14–22)	20 (17–23)	21 (15–26)	11.3	14.2	15.8
	BMI>2SD	24 (10–19)	20 (16–24)	23 (17–29)			
UK	1SD<BMI<2SD	18 (15–21)	19 (17–22)	20 (16–24)	7.6	9.4	10.1
	BMI>2SD	7 (5–9)	10 (8–12)	11 (8–14)			
Russia	1SD<BMI<2SD	11 (8–14)	12 (9–16)	14 (8–23)	4.4	5.8	7.9
	BMI>2SD	4 (2–5)	6 (4–8)	9 (3–17)			
Females							
Australia	1SD<BMI<2SD	20 (15–25)	21 (17–26)	21 (16–27)	8.5	9.9	10.5
	BMI>2SD	8 (4–12)	10 (6–14)	11 (7–16)			
USA	1SD<BMI<2SD	18 (15–22)	20 (17–23)	20 (15–25)	10.7	13.0	14.0
	BMI>2SD	13 (9–17)	17 (14–21)	19 (14–25)			
UK	1SD<BMI<2SD	20 (17–23)	21 (19–24)	22 (18–26)	8.4	9.7	9.8
	BMI>2SD	7 (5–10)	9 (8–11)	9 (7–12)			
Russia	1SD<BMI<2SD	10 (7–12)	11 (8–14)	13 (8–20)	3.5	4.2	5.3
	BMI>2SD	2 (2–3)	3 (2–4)	4 (1–9)			

[a]Reference 8.
[b]Reference 10.

independent estimate, and from 11 to 13% in the conservative estimate.

The results of the sensitivity analyses are presented in Supplementary Tables S1 and S2, available as Supplementary data at *IJE* online.

Discussion

According to our modelling, a not insubstantial proportion of incident MS risk could be prevented by eliminating smoking and especially high childhood BMI; despite significant assumptions this cannot be ignored. The proportion

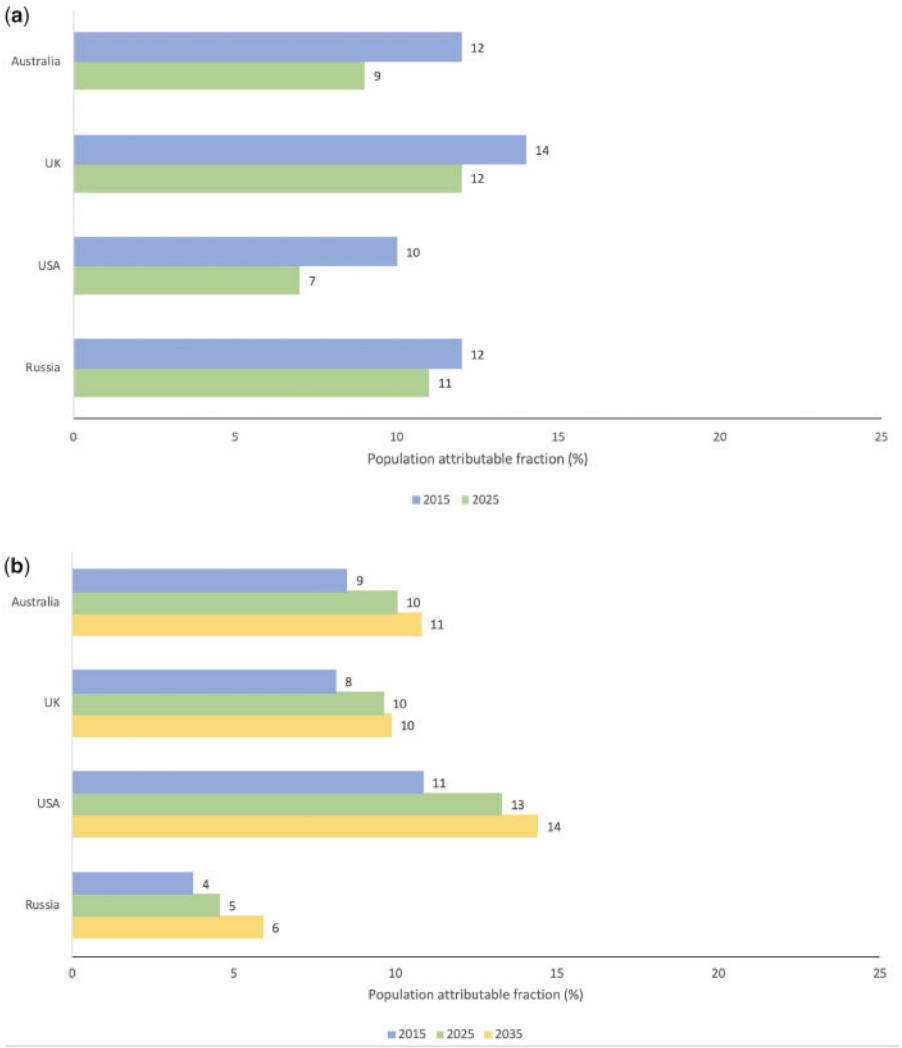

Figure 1 Proportion of incident MS attributable to (a) smoking and (b) childhood and adolescent high BMI

of incident MS attributed to smoking is projected to decline over time across all countries due to declining smoking rates, but the proportion attributed to high BMI is protected to increase due to rises in childhood obesity. Childhood obesity is projected to contribute up to 14% of overall MS risk in 2035. This highlights the need to act urgently to prevent childhood obesity; whereas cancer and cardiovascular disease occur in later adulthood, MS onset in young adulthood may have increased resonance with younger individuals.

This study is not without limitations, many of which arise from the assumptions inherent in this work. The PAF does not address the probability of causation, nor does it enable epidemiologists to discriminate between cases caused by, and those not caused by, the risk factors under consideration.[11] PAFs assume direct causality of risk factors, whereas an individuals' MS risk almost certainly results from risk factor interaction in a genetically susceptible population. Detailed characterization of time-dependent relationships between risk factors and MS do not exist, and PAF estimates are affected by the time-lags used. However, the PAFs we provide are based on population observations and are likely of the correct order of magnitude. They facilitate conceptualization of the impact of changing population characteristics on longer-term downstream risk. Analyses were weighted on the basis of a 3:1 female:male sex ratio, which is in keeping with current observations;[16] different sex ratio estimates may give different results.

The PAFs we present are based on RRs/odds ratios taken from existing literature, and there is the possibility of residual confounding, reverse causality or ascertainment bias. Synergistic effects between smoking and high BMI could not be considered, as high-quality prevalence estimates of combined exposure and MS risk are not available. The population in which these two risk factors overlap

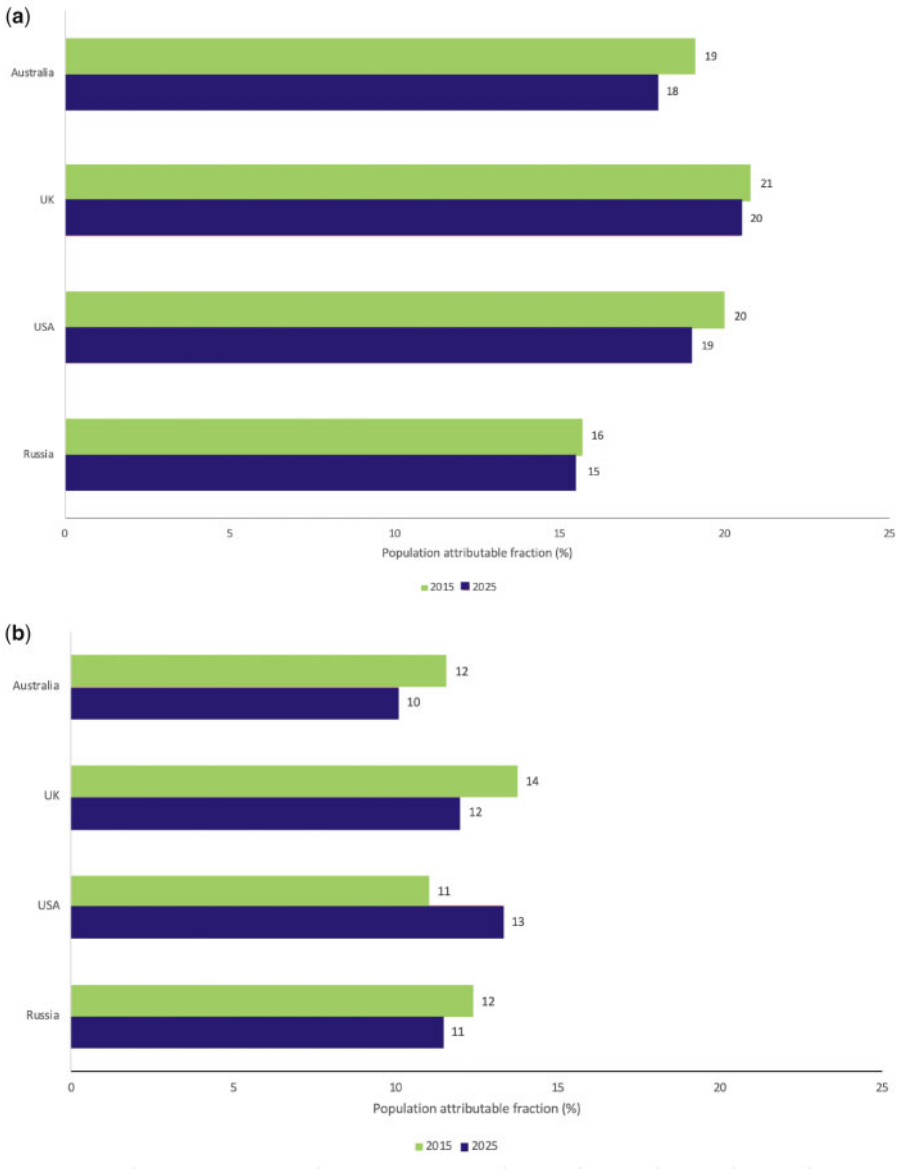

Figure 2 Proportion of incident MS attributable to smoking and childhood and adolescent high BMI combined in (a) independent and (b) conservative estimates

may well have significantly increased MS risk, particularly in the presence of additional MS risk factors. The use of a Mendelian randomization study to examine BMI could be argued to limit the applicability of the results, as it represents an indirect measure of genetically determined BMI rather than a direct measure of BMI. However, the point estimate of the RR associated with MS is similar, or more conservative, to that seen in population-based studies.[17,19] Studies that provide a direct RR estimate of the association between childhood/adolescent BMI and subsequent MS risk are either relatively small or use definitions of BMI categorizations not compatible with global prevalence estimates.[17,18] Categorizing risk factor exposures, rather than treating them as continuous variables, may result in an overestimation or underestimation of PAFs, but this was necessary to facilitate calculations using risk factor prevalence estimates defined with categorical measures.[12,13]

In conclusion, if causal, reducing the prevalence of these modifiable lifestyle risk factors is likely to have an important impact on MS incidence, as well as on other noncommunicable diseases. These data indicate the magnitude of the problem and highlight the need to act urgently. They inform the MS community of potential gains in MS prevention from joining forces with existing preventive campaigns to tackle the leading drivers of premature morbidity and mortality.

Supplementary Data

Supplementary data are available at *IJE* online

Author Contributions

J.P. proposed the study and wrote the first draft of the manuscript. J.P. and R.D. designed the analysis, which was conducted by J.P. All authors contributed to the interpretation of the data. All authors edited the manuscript for important intellectual content.

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Conflict of Interest

All authors declare no competing interests directly related to this research. Interests with no direct relation to the submitted manuscript are given below for the purposes of transparency:

J.P.: advisory board: Merck Serono; consultancy: Oxford Health Policy Forum CIC (with support from Novartis and F.Hoffmann-La Roche). K.S.: speaking honoraria and/or advisory boards: Novartis, Biogen, Teva, Merck Serono, Sanofi-Genzyme. G.G.: advisory boards: Merck Serono, Biogen Idec, Vertex Pharmaceuticals; editorial board: Multiple Sclerosis; speaker honoraria: Bayer Schering Pharma, Merck Serono, Biogen Idec, Pfizer, Teva Pharmaceutical Industries, Vertex Pharmaceuticals, Genzyme, Ironwood, Novartis; consultancy: Bayer Schering Pharma, Biogen Idec, GlaxoSmithKline, Merck Serono, Protein Discovery Laboratories, Teva Pharmaceutical Industries, UCB, Vertex Pharmaceuticals, GW Pharma, Novartis, FivePrime; speakers bureMerck Serono; research support: Bayer Schering Pharma, Biogen Idec, Merck Serono, Novartis, UCB, Merz Pharmaceuticals, LLC, Teva Pharmaceutical Industries, GW Pharma, Ironwood. J.C.: none declared. R.D.: advisory boards: Merck Serono, Biogen. Speaker honoraria: Teva, Biogen Idec. Travel: Sanofi Genzyme, Novartis, Teva, Biogen Idec. Research support: Biogen Idec, Barts Charity, MS Society UK.

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