Journal of Infection and Public Health 13 (2020) 1517–1521

Contents lists available at ScienceDirect

Journal of Infection and Public Health

journal homepage: http://www.elsevier.com/locate/jiph

Original Article

Strong association between adolescent obesity and consumption of macrolides in Europe and the USA: An ecological study

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ARTICLE INFO

Article history:
Received 3 January 2020
Received in revised form 12 May 2020
Accepted 17 June 2020

Keywords:
Childhood obesity
Macrolides
Antimicrobial resistance
Stewardship
Antibiotic
Azithromycin

ABSTRACT

Background: The reasons underpinning the large variations in the prevalence of childhood obesity are inadequately understood. Individual level studies have found that macrolide consumption at a young age increases the risk of subsequent obesity. We hypothesized that differences in population level consumption of macrolides may explain part of the variation in the prevalence of childhood obesity.
Methods: Mixed effects beta regression was used to assess the association between the prevalence of childhood obesity in countries in Europe/ states in the United States and population level consumption of macrolides and total antibiotics. Different time lags between consumption and obesity measurement were used.
Results: We found that in both the USA and Europe, population level consumption of macrolides was positively associated with subsequent childhood obesity prevalence. According to our model, the observed differences in population-level macrolide consumption in Europe/USA would translate into a 13%/72% higher odds of childhood obesity 5 years later. The association held regardless of the lag period used between exposure and outcome. The association with total antibiotic consumption was more equivocal.
Conclusions: Reducing macrolide consumption to that of low consumption countries may result in considerable reductions in childhood obesity.

Background

Excessive antibiotic consumption may be one of the many factors implicated in the epidemic of childhood obesity afflicting many populations around the world [1]. Antibiotics have been shown to alter the gut microbiome in ways that can lead to weight gain and obesity [2,3]. Antibiotics have been also found to result in weight gain of 8%–15% in a range of animals - an effect that is mediated by alternations in the gut microbiome and subsequent alterations in host metabolism [2–5].

There is still controversy about the role of antibiotics in weight gain in humans [6,7]. A meta-analysis found that antibiotic exposure at less than two years age was associated with a higher risk of overweight and obesity in later childhood [8]. Importantly, a dose effect was found such that each extra course of antibiotics increased the risk of obesity by 6%. Subsequent studies have both confirmed and contested the association between antibiotics and weight gain [7,9]. A number of studies have found that macrolides exert the largest effect on childhood obesity. A longitudinal study in children in Finland, for example, found that macrolides had the largest impact on weight gain and that this effect was largely mediated by marked changes in the intestinal microbiota which persisted long term post macrolide use [9]. This effect was found to apply independent of the age of the children [9]. Findings from cohort studies have varied somewhat [10] but a number of studies have found macrolides to exert the strongest effect on body mass index (BMI) and for this effect to peak in the mid-teens [9,11,12].

Ecological studies are a complementary way to assess if antibiotics are obesogenic and if so to what extent? Whilst studies from the USA have speculated about an ecological association [13] only one study that we are aware of has tested this association. This was a study in Europe that found a strong positive association between national childhood obesity and consumption of macrolides and weaker associations with quinolone and cephalosporin consumption [14]. Their conclusions are weakened by certain features of

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https://doi.org/10.1016/j.jiph.2020.06.024

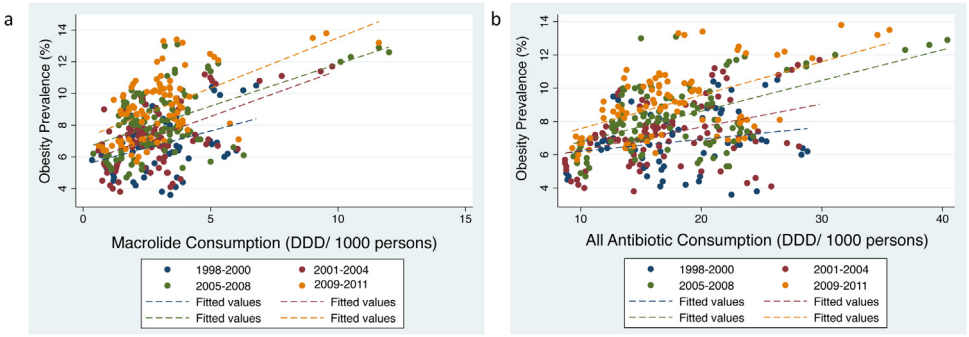

Fig. 1. Scatter plots and fitted lines of relationship between the prevalence of childhood obesity (Body Mass Index ≥30 kg/m^2; 0-19 years) and 5-year prior macrolide consumption (a) and total outpatient antibiotic consumption (b; both reported as defined daily doses/1000 population/ year) in 30 European countries between 1998 and 2016.

their study design. They used Pearson's correlation to assess the correlation between the national prevalence of childhood obesity in a single year (2010) and average outpatient consumption of 4 classes of antibiotics over a 22-year period (1997–2009). Their obesity estimates were also taken from a number of different sources which is not optimal.

We aimed to expand on this previous analysis by comparing the association between total antibiotic and macrolide consumption and obesity in both Europe and the USA using mixed effects models and standardized data spanning over two decades.

Methods

Data

Antimicrobial consumption

Europe. Data from the European Surveillance of Antimicrobial Consumption (ESAC) were used as a measure of national general population-level antimicrobial drug consumption [15,16]. ESAC provides open access to the data it collects on antimicrobial use in ambulatory care and hospital care in 31 European countries [15,16]. ESAC reports antimicrobial consumption as the number of defined daily doses (DDD) per 1000 inhabitants (DID) following the World Health Organization guidelines [16,17]. One DDD is defined as the average maintenance dose per day for a drug used in its main indication for adults [16]. ESAC does not provide data stratified by population age. The data provided by ESAC has been shown to be accurate and to correlate closely with that produced by other methodologies [16]. In our study, we used two measures of country-specific antimicrobial drug use in ambulatory care: total use and macrolides. Data was available from 1998 to 2018.

USA.

Data for all ages. State-level estimates of total number of all outpatient antibiotic and macrolide prescriptions per 1000 population were obtained from the CDC's Antibiotic Resistance & Patient Safety Portal (ARPSP; https://arpsp.cdc.gov/explorer).

The data are based on IQVIA estimates and reflect all outpatient antibiotic prescriptions dispensed to humans from community pharmacies. They do not include antibiotic prescriptions dispensed from federal facilities.

Data for 0–19 year olds in 2013. The CDC does not provide age specific data. We obtained state-level prescription data limited to those aged 0−19 years from a paper that reported total antibiotic and azithromycin outpatient prescriptions for this age group for the year 2013 [18]. The data was based on the same IQVIA estimates as the ARPSP data. We used Pearson's correlation to assess the correlation between antibiotic consumption in 0−19 year olds and the whole population in 2013.

Obesity prevalence

Obesity was defined as a BMI ≥ 30 kg/m^2.

Europe. Crude estimates for the national prevalence of obesity in 5–9, and 5–19 year olds were taken from the World Health Organizations Global Health Observatory data repository. Annual estimates are available from 1975 to 2016 (http://apps.who.int/gho/data/view.main.BMIPLUS2C05-19v). These estimates are based, in part, on the WHO European Childhood Obesity Surveillance Initiative that measures standardized weight and height measurements from over 300 000 children across the WHO European Region every three years. This data provides nationally representative data for participating countries [19].

USA. The CDCs Nutrition, Physical Activity, and Obesity data portal provides state-level annual prevalence estimates for obesity in adults (over 18 years) and adolescents (defined as those in grades 9–12) for the years 2011, 2013, 2015 and 2017 (https://www.cdc.gov/nccdphp/dnpao/index.html).

Analysis

Correlation between antibiotic consumption and obesity

Because the outcome variable was in the form of a proportion, mixed effects beta regression was used to assess the correlation between antimicrobial consumption and the prevalence of obesity 5 years later [20,21]. The beta regression models were built with the Generalized Linear Mixed Models Template Model Builder in R V.1.2.5019 [22]. The analyses were conducted in both the USA and Europe separately for all antibiotics and macrolides/azithromycin consumption. In general, there was a decline in antibiotic consumption over the study period (Figs S1, S2, S4 and S5). To control for this, the 'year' that antimicrobial consumption was measured was included as an explanatory variable in all analyses.

The following mixed effects beta regression model was used:

(Obesity in year Y and country/state C) ~ (antimicrobial consumption in year Y-5 and country C) + (year) + (random intercept for country/state C) + intercept + error.

Two types of sensitivity analyses were conducted. Firstly, the effect of using different lag periods (between antibiotic consumption and obesity prevalence) were assessed: 2, 8, 11, 14 and 17 years. In the case of the USA the data spanned 6 years and thus only the 2-year lag analysis could be performed. Secondly, we repeated the analyses limited to obesity prevalence in the 5−9 year category. This data was only available for the European region. Because the data from Europe, spanned such a long period we also stratified the analyses by 4-year periods. Because the association did not vary much between time periods we only show the stratified analyses in visual form (Fig. 1).

Table 1
Multivariable beta regression results for the association between consumption of antibiotics and prevalence of obesity in children in 30 countries in Europe (0–19 years) and 48 states in the USA.

	M1, Coef. (SE)	M2, Coef. (SE)	M3, Coef. (SE)
Europe			
Macrolides	0.030 (0.005)***	NA	0.06 (0.006)***
All antibiotics	NA	−0.006 (0.002)**	−0.027 (0.002)***
Year	0.028 (0.001)***	0.0294 (0.001)***	0.027 (0.0009)***
N	368	368	368
USA			
Macrolides	0.003 (0.0006)***	NA	0.0009 (0.001)
All antibiotics	NA	0.0007 (0.036)***	0.0005 (0.0003)
Year	0.056 (0.010)***	0.037 (0.009)***	0.042 (0.0129)***
N	73	73	73

*P < 0.01, **P < 0.001, ***P < 0.0001.
SE – Standard Error, NA – Not Applicable, M1 – model includes macrolide consumption and year, M2 - model includes total antibiotic consumption and year, M3 - model includes macrolide, total antibiotic consumption and year.

We assumed that all missing data was missing completely at random and therefore all missing data points were dropped from the analyses. All statistical analyses were performed in R V.1.2.5019 and Stata 16.0.

Results

Variations in antibiotic consumption

There were large variations in macrolide consumption between European countries in 1997 (median 2.9 DID, IQR 1.8–3.4 range 1.0–5.2) and US states in 2011 (median 192 prescriptions/1000 population, IQR 161–217, range 120–300). Differences in total antibiotic consumption were similarly large: Europe - median 18.1, IQR 11.8–22.2 range 9.0–27.9; USA - median 908, IQR 746–1006, range 588−1355. Macrolide consumption declined in all states in the USA until by 2017 median state level consumption had dropped 26%–142 prescriptions/1000 population (IQR 119–234; Fig S1). The decline in total antibiotics consumed was less marked (Fig S2) as was the decline in macrolide and total antibiotic consumption in European countries (2018 – macrolides: median 2.8 DID, IQR 1.9–3.6, range 0.5–6.4; all antibiotics median 17.2, IQR 13.2–20.8; Figs S4 and S5).

Association between antibiotic consumption in whole population and children

In the USA, the state-level consumption of azithromycin and total antibiotics in children (0−19 years) was strongly positively associated with that in the whole population in 2013 (R = 0.93, P < 0.001 and R = 0.98, P < 0.001, respectively).

Increase in childhood obesity

The prevalence of childhood obesity in European countries increased from median 1.7% (IQR 1-2.7%) in 1975 to a median 5.5% (IQR 3.6–6.5) in 1998, 7.9 (6.7–9.2 %) in 2011 and 9.1% (IQR 8.1-10.8%) in 2016 (Fig S6). In the US states, the prevalence of obesity increased from a median 12.1% (IQR 11.0-14.7%) in 2011 to a median 14.3% (IQR 12.7-16.7%) in 2017 (Fig S3).

Association between antibiotic consumption and obesity

In both Europe (coef. 0.03, SE 0.005, P < 0.001) and the USA (coef. 0.003, SE 0.0006, P < 0.001) azithromycin/macrolide consumption was positively associated with obesity 5 years later, Table 1, Fig. 1). These effect sizes would mean that the difference in macrolide consumption in Europe (4.2 DID)/USA (180 prescriptions/1000 population) in 1997/2011 would translate into a 13%/72% higher odds of childhood obesity 5 years later, respectively.

In the USA, total antibiotic consumption was also positively associated with 5-year lagged obesity (coef. 0.0007, SE 0.0001, P < 0.001). In Europe this association was weakly negative (coef.−0.006, SE 0.002, P < 0.01).

In Europe but not the USA, the effect sizes of both macrolide and all-antibiotic consumption increased in the model assessing the combined effects of macrolides and all antibiotics on obesity prevalence (M3, Table 1).

Effect of different time lags

Sensitivity analyses using a 2-year time lag increased the number of observations included in the models and produced similar results for the USA and Europe (Tables S1 and S2). The 8, 11, 14 and 17-year lag analyses produced similar results in Europe with the exception of the association between obesity and all antibiotics slowly switching to a positive direction (Table S2).

Associations with prevalence of obesity in 5–9 year olds

Repeating the analyses with the prevalence of obesity in 5–9 year olds revealed very similar results, with macrolide consumption being positively associated with obesity in the 2, 5 and 8-year lagged analyses (Table S3).

Discussion

We found that in both the USA and Europe, population level consumption of macrolides was positively associated with subsequent childhood obesity. This association held regardless of the lag period used between exposure and outcome. These findings are compatible with experimental animal studies and longitudinal cohort studies in humans that have found that macrolide ingestion in childhood can result in obesity mainly through alterations in the gut microbiome/host metabolism [5,23].

The relationship between total antibiotic consumption and obesity varied between the USA and Europe, being positive in the USA and negative or non-significant in Europe. There were a number of differences in the data from the USA and Europe which may be relevant here. The USA data covered a considerably shorter period than that from Europe, was reported in prescriptions as opposed to defined daily doses per capita and macrolide consumption was more closely correlated with total antibiotic consumption in the USA than Europe (Tables S4 and S5). Although the percentage of all antibiotics comprised by macrolides did not differ much between the USA (state median 18.4% [IQR 17.5-19.4%]) and Europe (country median 17.2% [12.6-20.7%]), the rate of decline in macrolides and total antibiotic consumption was faster in the USA (Figs S1 and S4 and Tables S4 and S5). Of note, at all time points, the prevalence of obesity was higher in the USA than Europe. Studies have found that by age 3, the average child in the USA in 2010 had consumed 3 courses of antibiotics and 17 courses by age 20, a figure that is higher than at least certain European countries [1,18]. The second most common antibiotic used for children in the USA was azithromycin [18]. It is thus possible that differences in antibiotic consumption between the USA and Europe explain the differences in the relationship between total antibiotic consumption and obesity between the two regions (Fig. 2).

A further important limitation is that apart from year, we did not control for other possible confounders such as differential prevalence of infectious diseases or genotypes associated with obesity. An optimal study design would have included antibiotic consumption data in children and used data from the period before the

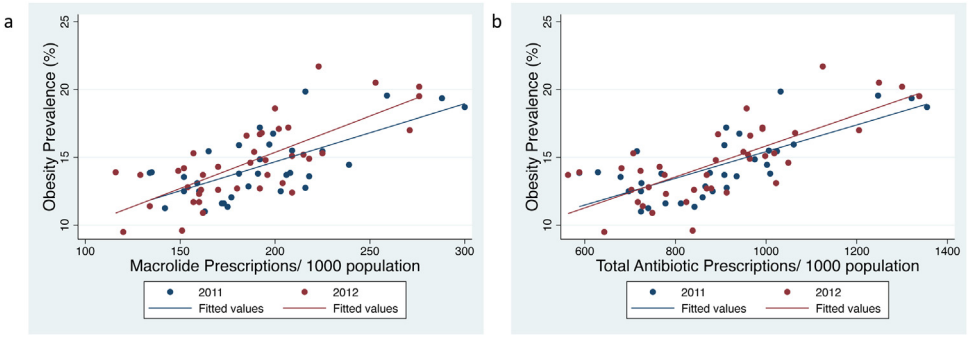

Fig. 2. Scatter plots and fitted lines of relationship between the prevalence of childhood obesity (Body Mass Index ≥30 kg/m^2; grades 9-12) and 5-year prior macrolide consumption (a) and total outpatient antibiotic consumption (b; both reported as prescriptions/ 1000 population/ year) in 48 states from the United States of America between 2011 and 2017.

increase in childhood obesity. Other shortcomings of our data include the lack of data on other sources of antimicrobial exposure that may be relevant such as maternal perinatal exposure which may alter the microbiota transferred to newborns [1], and antimicrobial consumption via food, toiletries and water [1,24]. These omissions should however result in a misclassification bias which typically leads to false negative rather than positive results. Our study was by design ecological and is thus susceptible to the ecological inference fallacy. The fact that other studies have found analogous effects at an individual level reduces but does not eliminate this risk. We were also unable to assess the effect of specific macrolides on obesity.

The effect sizes we found were not small. Differences in macrolide consumption in Europe, for example, varied 5-fold in 1997 and 11-fold in 2016, whilst the prevalence of childhood obesity varied around two-fold. In 2016, the prevalence of obesity (13.8%) and macrolide consumption (6.1 DID) were both highest in Greece whereas both obesity (6.7%) and macrolide consumption (0.54 DID) were lowest in Sweden. Both countries held their respective positions for most of the period between 1997 and 2016. According to our model, the annual differences in macrolide consumption would translate into around a 13% higher odds of childhood obesity five years later. A number of analyses have found that differences in antibiotic consumption between high-income populations are not determined by differences in clinical indications for antibiotics but rather by a range of structural, contingent and cultural factors [1,15,18,25–27]. They are however amenable to a range of interventions [25,28]. Given the range of adverse health effects associated with childhood obesity [29], our findings therefore provide a new rationale for strengthening proven antibiotic stewardship interventions in high macrolide consumption populations [28].

Our findings thus contribute to a growing body of evidence demonstrating that excess macrolide and antibiotic consumption is associated with a wide range of adverse outcomes [1,30,31]. Undoubtedly one of the most important of these is antibiotic resistant infections which may kill more people per year than cancer by 2050 [32]. The argument that we should reduce the use of antibiotics in order to prevent antibiotic resistance has however been found to have limited traction on both doctors and patients [33,34]. This may be particularly the case in settings such as that of a child with an upper respiratory infection where the parents expect antibiotics [33]. In such cases it may be more efficacious to focus on the negative long-term health effects of unnecessary antibiotic use for the child. One approach could be to explain to the parents that if one was in a low antibiotic consumption population, such as Sweden, one would very likely not be given an antibiotic for this indication and that the no-antibiotic approach results in healing as quickly but without all the adverse effects of receiving antibiotics such as unwanted weight-gain and selection for antibiotic resistance [1,32]. Taken in conjunction with the findings of other studies [9,11,12], our findings are also supportive of guidelines that advocate the use of more narrow spectrum antibiotics rather than broader spectrum antibiotics such as macrolides whenever possible [28,35].

Data availability

With the exception of the data pertaining to antibiotic consumption in 0–19 year olds in the USA, the data we used is publicly available from the web sources outlined in the methods section.

Funding

No funding sources.

Competing interests

None declared.

Ethical approval

Not required.

Acknowledgements

We would like to thank Katherine E. Fleming-Dutra from the Centers for Disease Control and Prevention, Atlanta, for providing us with antimicrobial consumption data for 0 to 19 year olds.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jiph.2020.06.024.

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