ORIGINAL ARTICLE

Association of Long Term Antibiotic Use and Diagnosis of Chronic Disease

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Abstract

Background: There has recently been increasing interest in the role of the human microbiome in disease. Antibiotic use is known to disrupt the intestinal microbial environment and cause acute disease, for example pseudomembranous colitis. This study aimed to investigate the hypothesis that long-term antibiotic use is associated with the development of chronic diseases, i.e., Asthma, Rheumatoid Arthritis, Inflammatory Bowel Disease, Colorectal Cancer, and Dementia.
Methods: The study is a retrospective observational study using ontologically defined cases recorded by primary care physicians covering the period 2004 to 2015 combined with prescribing data. The study is primary care based, utilizing records held by the Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC) database, representative of all English General Practices, over the period 2004 to 2015 inclusive. All patients registered with practices subscribing to the RCGP RSC database, with 10 years of prescribing history and other full demographic information required for the study recorded, numbering 644,273 were utilized. All records were analyzed for demographic data, diagnoses of study, known risk factors, and prescribing history of antibiotics. Exclusion criteria included incomplete data for known risk factors or demographics. The main outcome measures are the odds ratios (OR) of being diagnosed with one of the diseases of the study per antibiotic prescription issued over the preceding decade before diagnosis, adjusted for demographics and known risk factors.
Results: The OR (2.5% CI, 97.5% CI) of being diagnosed with Asthma was 1.004 (1.002, 1.006), Rheumatoid Arthritis 1.006 (1.003, 1.008), Inflammatory Bowel Disease 1.007 (1.006, 1.008), Colorectal Cancer 1.001 (0.999, 1.002), and Dementia 1.001 (0.998, 1.001).
Conclusions: The long-term use of antibiotics is associated with a *statistically significant dose related increase in the odds of being diagnosed with asthma, rheumatoid arthritis and inflammatory bowel disease*, but not all forms of dementia or colorectal cancer. Potential mechanisms include chronic disruption of the microbiome. This finding has implications for practitioners who prescribe antibiotics, the pharmaceutical industry, policy makers, and researchers involved in studying chronic disease mechanisms.

Keywords: Antibiotics; Chronic Disease; Microbiome

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INTRODUCTION

The association of antimicrobial use with the increasing development of antimicrobial resistance has been previously described and is now widely considered to be a serious global health problem (1). Use of antibiotics can upset the human gut microbiome, resulting in acute disease. However, treatment of the pathogenic organism with antibiotics can result in a cure. Replacement of the disrupted microbiome with 'normal', non-antibiotic treated gut flora in the form of fecal matter transplants can also yield excellent therapeutic results, as in the case of *C. difficile* diarrhea (2).

However, the role of the microbiome as an etiologic single entity factor in human disease is a relatively uncharted territory. The idea that a dynamic and inter-related community of diverse micro-organisms living in discrete body compartments, such as the gut and respiratory tract, might be involved in the pathogenesis of disease has been investigated in only a few conditions including:

1. Inflammatory bowel disease (3)
2. Colorectal cancer (4)
3. Allergic and immune diseases including asthma (5)
4. Obesity (6)
5. Vascular disease (7).

Much of this work has been at the molecular and cell signaling pathways level; however, there is sparse epidemiological evidence that long term disturbance of the

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microbiome might contribute to the development of chronic disease. Here, we study the long-term use of antibiotics that may alter the microbiome in relation to chronic disease, looking for epidemiological evidence of the association between antimicrobial use and the development of asthma, rheumatoid arthritis, inflammatory bowel disease, colorectal cancer, and dementia (including vascular dementia).

METHODS

This retrospective observational study data set was drawn from the RCGP RSC, which hosts data as a pseudonymized [virtually anonymized – no names are held but demographic and medical record data are; identification is virtually impossible; data is encrypted and stored on dedicated secure servers at the University of Surrey. The secure network at University of Surrey meets the NHS information security standard for holding these data as set out in the Information Governance toolkit] dataset from a nationally representative sample of 644,273 people registered with the network practices of all ages (range approximately 0 – 100) (8). The database has been involved in surveillance of influenza and respiratory disease for over 50 years. Over this period, practices have had feedback about their data quality, in particular the differentiation of new (incident) cases from follow-up consultations. Data quality is as good as any other existing dataset held for routine primary care (9).

UK general practice is suitable for this type of study because it has a registration-based system with patients registered with a single practice. Practices have been computerized since the late 1990s, with pay-for-performance introduced in 2004 for chronic disease management. Key data are coded 10, which include diagnoses, therapy, test results, and other key data. Ethics approval was not required for this study, as determined by the Medical Research Council Heath Research Authority decision tool.

Antibiotic codes were searched using the UK's most ubiquitous electronic medical record for primary care, Egton Medical Information Systems (EMIS) and Read v2 drug codes, to capture prescribing using the different Electronic Medical Record (EMR) systems. Suitable diagnoses and known risk factors were defined ontologically.

Association of chronic antibiotic prescribing with disease was tested by interrogating the dataset for new cases of asthma, colorectal carcinoma, rheumatoid arthritis, dementia, inflammatory bowel disease, and known risk factors for these diseases. New cases were defined as records in which the first recorded diagnosis in the EMR appeared in 2015, represented by the recording of clinician assigned diagnostic codes in the EMR in that year. Antibiotic load was defined as the sum of antibiotic prescriptions issued in the preceding ten years. Dates were chosen to ensure that 10 years of complete data were available.

Risk factors, e.g. smoking, diabetes, hypertension, and relevant family history were identified through literature searches and ontologically defined. Records were searched for the occurrence of risk factors at any point in time within the subject record.

New cases were combined with demographic data, known risk factors for the diseases in question, and the number of antibiotic prescriptions in each of the preceding ten years to create the diseases-specific datasets and total antibiotic load in the entire period (sum of each of the preceding ten years' prescriptions). The independent risk factors for the diseases are shown in Table 1. The selection of subjects for regression model data frames is shown schematically (Figure 1).

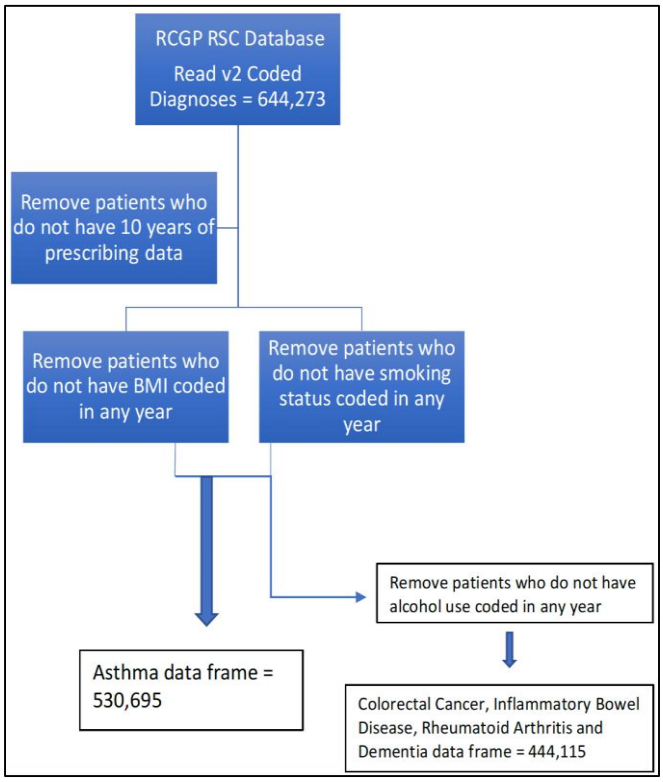

Figure 1. Regression model data frame construction
BMI = Body Mass Index
RCGP = Royal College of General Practitioners
RSC = Research & Surveillance Center
Read v2 = version 2 Read computer codes for general practice computerized record systems.

Statistical analysis

Multiple logistic regression analysis was undertaken using R studio version 1.0.153 to control for demographic variables and known risk factors.

The logistic regression model yielded an estimate of the odds ratio (OR) of being diagnosed with one of these diseases

Table 1. Independent Risk Factors for Disease

Baseline Independent Variables	Rheumatoid Arthritis	Dementia	Asthma	Bowel Cancer	Inflammatory Bowel Disease
Antibiotic Load	FH Rheumatoid Arthritis	Alcohol Hazardous	Atopy	Alcohol Hazardous	FH Inflammatory Bowel Disease
Age		Alcohol Safe	FH Atopy	Alcohol Safe	
Ethnicity B		Alcohol Non-Drinker	Eczema	Alcohol Non-Drinker	
Ethnicity M		Diabetes	FH Asthma	Familial Adenomatous Polyposis	
Ethnicity O		Atherosclerosis	Stress	Family History of Bowel Cancer	
Ethnicity W		Hypertension	Occupational Asthma	Inflammatory Bowel Disease	
Ethnicity Z		Down's Syndrome	Preterm Birth		
Ex-Smoker			Delivery by Cesarean Section		
Non-Smoker					
Gender					
IMD Decile					
BMI					

(defined as first diagnosis in the record in 2015) regressed against antibiotic prescribing load (sum of antibiotic prescriptions in the preceding decade), demographic variables, and other independent variables, i.e. known risk factors for the disease in question.

Logistic regression models were run against data frames that maximized the number of records; for example, if alcohol was deemed to be a risk factor that needed to be controlled for, records that had no record of alcohol intake were removed; otherwise the full dataset was used where each subject had the risk factor satisfactorily recorded. Records with no ethnicity, smoking, or BMI data were removed entirely. The basic logistic regression model fitted to the data is:

Disease First Recorded in 2015 ~ Total Antibiotic Load 2004-2014 + Ethnicity + Gender + Age + Smoking Status + IMD Score + BMI + Specific Disease Risk Factors

Log [(probability disease diagnosed in 2015)/(1-probability disease diagnosed in 2015)] = $ß_0$ + $ß_1$AntibioticLoad + $ß_2$Age + $ß_3$Ethnicity + …… + $ß_x$Risk Factor$_x$

RESULTS

The baseline dataset comprised 644,273 records. This was reduced to 444,115 when alcohol intake was included in the models (records with no alcohol intake coding were removed) and 530,695 with only smoking and BMI cleaned data (records with no BMI or smoking data recorded removed). Sample characteristics are shown in Table 2. There are some previously described differences between the RCGP RSC database and national population characteristics, e.g., the RCGP RSC population is slightly less obese and less deprived (as defined by the Index of Multiple Deprivation score, widely used in the UK), but disease prevalence is mostly identical to the national population (8). The total antibiotic prescription load for the decade is summarized in Table 3. Prescribing by year did not vary significantly from year to year.

The ORs of developing diseases after adjusting for known risk factors are shown in Table 4. The OR is the increase in odds *per antibiotic prescription* over the preceding decade, adjusted for age, gender, IMD decile and other known risk factors for the diseases. Table 3 shows sample characteristics compared to the sampling frame and national population.

The complete OR of disease development for each risk factor is shown in Tables 5-9. ORs in bold indicate significant risk factors at the 5% level.

Reference levels are: Asian, smoker, female, IMD Decile

Table 2. Sample Characteristics vs Sampling Frame and National Population. Standard deviation is shown in parenthesis.

	Total Population RCGP RSC Database	Census Data/ National Data All ages	Sample Data Alcohol, BMI & Smoking (NA removed)	Sample Data Smoking & BMI (NA removed)
Median Age in years	39.00 (23.20)	40.30 (~24.00)	47.00 (16.70)	44.00 (19.70)
Female (%)	50.60	50.70	54.50	50.6
Asthma Prevalence (%)	6.00	6.00	-	4.45
Dementia Prevalence (%)	1.00	1.00	0.51	-
White Ethnicity (%)	58.20	85.40	68.30	64.10

Table 3. Number of Prescriptions per Subject 2004-15

	Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
Asthma Model	0.0	1.0	4.0	7.8	8.0	571.0
Other Models	0.0	1.0	4.0	8.4	9.0	571

Table 4. Adjusted Odds Ratios of Disease Diagnosis vs Preceding Decade's Antibiotic Load

	Odds Ratio	2.5% Limit	97.5% Limit
Asthma	1.004	1.002	1.006
Rheumatoid Arthritis	1.006	1.003	1.008
Inflammatory Bowel Disease	1.007	1.006	1.008
Dementia	1.001	0.999	1.002
Bowel Cancer	1.000	0.998	1.001

Table 5. Asthma Model Output

	Odds	2.5% Limit	97.5% Limit
Total Antibiotics 2004 - 2015	1.004	1.002	1.006
Age	1.000	0.998	1.002
Ethnicity Code B	0.768	0.488	1.179
Ethnicity Code M	0.490	0.189	1.042
Ethnicity Code O	1.018	0.449	2.001
Ethnicity Code W	0.929	0.729	1.206
Ethnicity Code Z	0.727	0.565	0.951
2014Ex-smoker	0.851	0.765	0.948
2014 Non-smoker	0.704	0.627	0.791
Sex	0.867	0.796	0.943
IMD Decile	0.978	0.964	0.993
Atopy	1.419	1.271	1.582
FH Atophy	1.110	0.702	1.661
Eczema	0.917	0.796	1.054
FH Asthma	1.420	1.246	1.611
Stress	1.191	1.047	1.350
Occupational Asthma	0.000	0.000	0.0182
Born by Cesarean Delivery	0.705	0.117	2.189

B = black, M = mixed, O = other, W = white, Z = unknown. IMD = index of multiple deprivation, FH = family history.

Table 6. Rheumatoid Arthritis Model Output

	Odds	2.5%	97.5%
Total Antibiotics 2004 - 2015	1.006	1.003	1.008
FH RA Prior to 2015	3.926	1.400	8.522
Age	1.013	1.008	1.018
Ethnicity Code B	0.790	0.322	1.779
Ethnicity Code M	0.000	0.000	0.000
Ethnicity Code O	0.448	0.025	2.182
Ethnicity Code W	0.691	0.437	1.172
Ethnicity Code Z	0.589	0.363	1.018
2014Ex-smoker	0.764	0.619	0.948
2014Non-smoker	0.520	0.404	0.669
Sex	0.635	0.531	0.758
IMD Decile	0.963	0.935	0.992

B = black, M = mixed, O = other, W = white, Z = unknown. IMD = index of multiple deprivation, FH = family history, RA = rheumatoid arthritis.

Table 7. Inflammatory Bowel Disease Model Output

	Odds	2.5% Limit	97.5% Limit
Total Antibiotics 2004 -2015	1.008	1.006	1.009
Age	0.987	0.984	0.990
Ethnicity Code B	0.683	0.348	1.257
Ethnicity Code M	1.345	0.607	2.678
Ethnicity Code O	0.699	0.168	1.943
Ethnicity Code W	1.293	0.939	1.841
Ethnicity Code Z	1.186	0.854	1.700
2014 Ex-smoker	1.284	1.132	1.460
2014 Non-smoker	0.885	0.768	1.021
Sex	1.089	0.991	1.197
Alcohol 2014 Hazardous	1.068	0.837	1.384
Alcohol 2014 Non-drinker	1.170	0.905	1.535
Alcohol 2014 Safe	1.050	0.822	1.361
Family History of IBD	25.599	17.708	35.907
IMD Decile	1.014	0.997	1.031

B = black, M = mixed, O = other, W = white, Z = unknown. IMD = index of multiple deprivation, FH = family history.

1 (poorest), alcohol moderate (where applicable to model – inflammatory bowel disease, dementia and bowel cancer models).

DISCUSSION

This study demonstrates a statistically significant, dose-related, positive association between the odds of being diagnosed with asthma, rheumatoid arthritis, and inflammatory bowel disease and the total amount of antibiotics prescribed in the preceding decade in a representative sample of UK primary care patients, across all age ranges. The increase in odds of diagnosis is per antibiotic prescription, so an apparently small increase in the odds ratio becomes much larger in subjects who have received more prescriptions. For example, the odds of developing asthma, at 1.004, increase to 1.40, i.e., by 40% over the 10-year time

Table 8. Dementia Model Output

	Odds	2.5 % Limit	97.5 % Limit
Total Antibiotics 2004 - 2015	1.001	1.000	1.002
Age	1.128	1.122	1.133
Ethnicity Code B	1.034	0.570	1.825
Ethnicity Code M	0.884	0.261	2.262
Ethnicity Code O	2.128	0.899	4.481
Ethnicity Code W	0.877	0.624	0.128
Ethnicity Code Z	0.831	0.584	1.223
2014Ex-smoker	1.073	0.923	1.253
2014Non-smoker	0.976	0.823	1.158
Sex	0.945	0.859	1.039
Alcohol 2014 Hazardous	0.640	0.497	0.839
Alcohol 2014 Non-drinker	0.707	0.543	0.934
Alcohol 2014 Safe	0.665	0.515	0.873
Diabetes Before 2015	1.265	1.138	1.404
Atherosclerosis Prior to 2015	1.102	0.990	1.226
Hypertension Prior to 2015	1.153	1.045	1.273
IMD Decile	0.960	0.945	0.975

B = black, M = mixed, O = other, W = white, Z = unknown. IMD = index of multiple deprivation, FH = family history

Table 9. Bowel Cancer Model Output.

	Odds	2.5% Limit	97.5% Limit
Total Antibiotics 2004-2015	1.000	0.999	1.001
Age	1.046	1.044	1.048
BMI 2014	1.009	1.005	1.013
Ethnicity Code B	1.673	1.187	2.356
Ethnicity Code M	1.512	0.871	2.490
Ethnicity Code O	1.144	0.552	2.124
Ethnicity Code W	2.041	1.622	2.614
Ethnicity Code Z	1.830	1.450	2.349
2014 Ex-smoker	0.881	0.827	0.938
2014 Non-smoker	0.794	0.740	0.853
Sex	1.264	1.208	1.323
Alcohol 2014 Hazardous	0.839	0.751	0.940
Alcohol 2014 None	0.715	0.633	0.809
Alcohol 2014 Safe	0.743	0.664	0.834
IMD Decile	1.012	1.004	1.021
FAP Prior to 2015	1.054	0.059	4.876
FH of CRC	1.128	0.858	1.451
IBD Prior to 2015	1.099	0.907	1.318

B = black, M = mixed, O = other, W = white, Z = unknown. IMD = index of multiple deprivation, FH = family history.

period if 100 antibiotic prescriptions in the preceding decade were issued (equating to 10 prescriptions per year). No such association was seen for colorectal cancer or dementia. On a population basis, this implies that if there is indeed a causal relationship, that antibiotic prescribing may be a significant driver of chronic disease.

A possible common link is modulation of the microbiome and its long-term disruption by repeated administration of antibiotics. Relevant mechanisms might include the overgrowth of pathogenic organisms (as in the case of antibiotic associated pseudomembranous colitis), the disturbance of particular metabolic pathways to produce pathogenic molecules and the decimation of protective organisms. If proven, it may be that a proportion of total cases of these diseases is iatrogenic. The implications add weight to efforts to reduce antibiotic use and may be a useful public health message for policy makers to inform the public and perhaps help change patient expectations during physician encounters. More than that, if there is a true causal association between antibiotic prescribing and chronic disease, the finding is relevant to prescribers, researchers considering the mechanisms of disease causation, regulators governing the issuance of antibiotics, the government and the pharmaceutical industry undertaking post-marketing surveillance of drug safety.

CONCLUSION

The demonstrated association is a statistically significant dose-related increase in the OR of being diagnosed with asthma, rheumatoid arthritis, or inflammatory bowel disease across all age ranges in a sample of subjects drawn from patients registered with English general practices. Potential mechanisms include chronic disruption of the microbiome. This finding has implications for practitioners who prescribe antibiotics, the pharmaceutical industry, policy makers, and researchers involved in studying chronic disease mechanisms. In summary, this study demonstrates a statistically significant positive association between the long-term use of antibiotics and the diagnosis of asthma, inflammatory bowel disease and rheumatoid arthritis which should be explored further by both epidemiological and basic sciences research.

LIMITATION

1. Patient de-registration during the period would bias the results towards the null as these patients would not have been coded as cases but might have had prescriptions. This is unlikely to be a significant effect, given the small number of de-registrations during the study period. Additionally, the results of three of the models are statistically significant despite this bias and may be greater in magnitude if it were not present.
2. It has been assumed that all the prescriptions issued were actually ingested as issued. If they were not actually taken, it would be hard to ascribe the effects described to the antibiotics.
3. The study grouped all antibiotics into one category. Given that antibiotics are in fact a very heterogeneous group of drugs, it may be that this biased the results towards the null. One might intuitively expect broad spectrum antibiotics to have a greater effect on changing the microbiome, but equally, narrow spectrum drugs might affect a particularly important microbe. It would be interesting to undertake further studies looking at individual drugs or groups of drugs by spectrum of activity.
4. The removal of some records might have led to some bias in the study. The characteristics of the removed data were examined in the case of those records which had no alcohol consumption recorded and were found to be a much younger group of patients, which might explain why no consumption had been noted by primary care practitioners. This subset would have been most unlikely to have developed dementia or bowel cancer, thus biasing the result away from the null. However, given the results for which these records were removed were non-significant in any case, it seems likely that inclusion of the records would not have affected the estimated ORs. As alcohol is not deemed to be a risk factor for asthma or rheumatoid arthritis, this would not have biased the results for these conditions.

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REFERENCES

1. WHO. Global Action Plan on Antimicrobial Resistance. Available from: https://www.who.int/antimicrobial-resistance/global-action-plan/en/
2. Rao K, Safdar N. Fecal microbiota transplantation for the treatment of Clostridium difficile infection. *J Hosp Med* 2016; 11:56-61.
3. Halfvarson J, Brislawn CJ, Lamendella R, Vázquez-Baeza Y, Walters WA, Bramer LM et al. Dynamics odf trhe human gut microbiome in inflammatory bowel disease. *Nat Microbiol* 2017;2:17004.
4. Sanapareddy N, Legge RM, Jovov B, McCoy A, Burcal L, Araujo-Perez F et al. Increased rectal microbial richness is associated with the presence of colorectal adenomas in humans. *ISME J* 2012;6:1858–68.
5. Russell SL, Gold MJ, Hartmann M, Willing BP, Thorson L, Wlodarska M et al. Early life antibiotic-driven changes in microbiota enhance susceptibility to allergic asthma. *EMBO Rep* 2012;13:440–7.
6. Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, Ley RE et al. A core gut microbiome in obese and lean twins. *Nature* 2009; 457:480–4.

7. Zhuye Jie, Huihua Xia, Shi-Long Z, Feng Q, Li S, Liang S et al. The gut microbiome in atherosclerotic cardiovascular disease. *Nat Commun* 2017;8:845.
8. Correa A, Hinton W, McGovern A, van Vlymen J, Yonova I, Jones S, et al. Royal College of General Practitioners research and Surveillance Centre (RCGP RSC) sentinel network: a cohort profile. *BMJ Open* 2016;6:e011092.
9. de Lusignan S, Correa A, Smith G, Yonova I, Pebody R, Ferreira F et al. RCGP Research and Surveillance Centre: 50 years' surveillance of influenza, infections, and respiratory conditions. *Br J Gen Pract* 2017; 67:440-1.