

ORIGINAL ARTICLE

Risk of fibromyalgia following antibiotic prescriptions: A population-based case–control study

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Abstract

Background: The health of the gut microbiome is now recognized to be an important component of the gut–brain axis which itself appears to be implicated in pain perception. Antibiotics are known to create dysbiosis in the microbiome, so whether fibromyalgia is more commonly diagnosed after antibiotic prescriptions provides a means of exploring the role of the microbiome in the experience of chronic pain.

Methods: A case–control study was carried out using electronic health records collected in the UK's Clinical Practice Research Datalink (CPRD), a comprehensive database of primary care consultations. For each case of diagnosed fibromyalgia, three controls were identified and matched by age, gender and GP practice. The exposure variable was the number and timing of antibiotic prescriptions over previous years. The analysis involved adjusting for a wide range of co-variates that might be possible confounders.

Results: A total of 44,674 cases of fibromyalgia were identified together with 133,513 controls. After adjusting for co-variates, it was found that both the total number of prescriptions and their timing was associated with an FM diagnosis. For example, the quartile with the highest number of prescriptions and that with the longest exposure had a greater than three-fold increase in FM diagnoses (number of prescriptions: odds ratio 3.92; 95% CIs: 3.71–4.13; exposure odds ratio 3.28; CIs: 3.13–3.43). Some antibiotics (such as tetracyclines and metronidazole) seemed to confer greater risk than others.

Conclusions: The results lend support for prior antibiotics being an important risk factor for a diagnosis of FM.

Significance: This study shows an association between the volume as well as timing of prior antibiotic prescriptions and of a subsequent diagnosis of fibromyalgia in primary care.

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1 | INTRODUCTION

Fibromyalgia (FM) or fibromyalgia syndrome is a common yet poorly understood condition. It is estimated to affect between about 2% and 8% of the world population and presents with chronic widespread musculoskeletal pain often accompanied by other symptoms, such as fatigue, intestinal disorders and alterations in sleep and mood. FM can be very distressing with suicidal ideations, suicide attempts and death by suicide all reported to be raised (Gill et al., 2021). It shares many of its symptoms—pain, fatigue, etc.—with other so-called medically unexplained symptoms such as chronic fatigue syndrome. Although FM is associated with a number of other conditions such as irritable bowel syndrome (IBS) (Erdrich et al., 2020a), obesity (D'Onghia et al., 2021), diabetes and insulin resistance (Pappolla et al., 2021; Zetterman et al., 2021) and inflammatory conditions such as rheumatoid arthritis and systemic lupus erythematosus its aetiology is for the most part unknown.

One emerging area of interest in the pathophysiology of FM is the relationship between the composition of the gut microbiome and the perception of pain (Alizadeh et al., 2023; Liu et al., 2023; Minerbi & Shen, 2022). Microbiome dysbiosis has been reported as being related to osteoarthritic pain, probably mediated through systemic inflammation (Binvignat et al., 2021; Drago et al., 2019; Sánchez Romero et al., 2021), as well as in pelvic pain (Salliss et al., 2021). Gut dysbiosis and its effect on the regulation of inflammation has been proposed as a factor in the experience of pain after spinal cord injury (Bannerman et al., 2021) and post-operative pain (Brenner, Shorten, et al., 2021). Pain after upper limb surgery under peripheral nerve block seems to be associated with gut microbiome composition and diversity (Brenner, Cherry, et al., 2021). The association of FM with functional gastrointestinal disorders (Erdrich et al., 2020a) offers support for the importance of the gut–brain axis in the experience of pain as well as reported changes in the microbiome in FM (Minerbi et al., 2023).

One recognized determinant of gut dysbiosis is the consumption of wide-spectrum antibiotics, but there are few studies of this risk for FM. Clinic attenders who were prescribed fluoroquinolones were more likely to report later fibromyalgia compared with those for whom the drug was not prescribed and a case–control study further showed that amoxicillin and azithromycin were equally significant as risk factors for FM (Ganjizadeh-Zavareh et al., 2019). These observations support a possible role for wide-spectrum antibiotics in the development of FM. We therefore examined this hypothesis further by conducting a case–control study in a large clinical database comparing the antibiotic history of patients diagnosed with fibromyalgia with a matched control group.

2 | METHOD

A case–control study was implemented in one of the world's largest primary care databases, the Clinical Practice Research Datalink (CPRD). CPRD currently contains medical records from 1800 general practices (24% of UK practices) capturing detailed clinical, therapeutic, lab test, immunization, referral and lifestyle data for over 60 million patients (~17 million active patients). CPRD has been granted generic ethics approval by the UK's Health Research Authority for observational studies that make use of only anonymized data and linked anonymized NHS healthcare data (ref. 21/EM/0265). Data are collected from contributing practices on a daily basis and processed to create monthly snapshots for clinical and epidemiological investigations (Wolf et al., 2019). The organization of the healthcare system in the UK (a publicly funded health service), where general practitioners are considered the 'gatekeepers' and coordinators of healthcare makes these data a valuable resource for epidemiological investigations. CPRD primary care practices are broadly representative of the UK population in terms of age, gender and general practice size distribution (Herrett et al., 2015). The data have been extensively validated for pharmaco-epidemiological, clinical and health service usage research (Armstrong et al., 2016; Dregan et al., 2014, 2019).

2.1 | Study population

Cases were patients aged 18 years and over with a recorded diagnosis of fibromyalgia between 1 January 2016 and 31 December 2021 using SNOMED/Read diagnostic codes. The index date was defined as the first date that a diagnosis of FM was ever recorded in a patient's medical record. Cases and controls had to have a minimum of 12 months of medical history in CPRD prior to the index date for FM and to have no history of FM at cohort entry. Three controls were sought for each case, individually matched on age (within 2 years to ensure sufficient matched controls per practice), gender and family practice; controls were given the index date of the FM diagnosis of their matched case. Incidence density sampling was used to select controls to minimize differential loss to follow up.

2.2 | Exposure

The exposure variable included any antimicrobial prescription (excluding anti-tuberculous and anti-leprotic drugs) prior to the FM index date. The class of a given antibacterial prescription was derived from subchapters

of the British National Formulary (Chapter 5.1) and included penicillins, cephalosporins, tetracyclines, sulphonamides, trimethoprim, metronidazole and quinolones. Information extracted included the class of antimicrobial prescriptions, the number of antimicrobial prescriptions issued during different prior follow-up periods (1, 2, 3, 4, 5, 6–10, >10 years) and the interval between the first antimicrobial prescription and the FM index date as measures of the extent of exposure.

2.3 | Confounders

Several variables that have been associated with FM risk and antibiotic prescribing were included as covariates. These included matching variables (age, gender and practice); body mass index (BMI) (<18.5, 18.5–25, >25 to <30, 30 to <35 and ≥ 35 kg/m²); lifestyle factors such as smoking (never, ex-smoker, current smoker); comorbidity including cancer, renal disease, autoimmune disorders (including rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disorders), chronic obstructive pulmonary disease (COPD), type 2 diabetes, cardiovascular diseases (including stroke and heart failure) and co-prescribing within 3 months from index date for FM including use of immunosuppressive therapies, corticosteroids and non-steroidal anti-inflammatory drugs. For comorbidities, body mass index (BMI) and lifestyle factors, the value closest to the index date for FM was included.

2.4 | Statistical analysis

Our analyses were restricted to patient-level data from the Aurum version of the CPRD database (Wolf et al., 2019). Descriptive analyses (e.g. frequencies, means) were used to compare baseline characteristics between cases and controls. Data were collected from the earlier of date of registration with the general practice or the date of first antibiotic prescription and continued until the index date for FM (case index date for matched controls). Conditional logistic regression was used to estimate the odds ratios (ORs) and 95% confidence intervals (95% CIs) for FM risk associated with previous antimicrobial exposure. In addition to the matching variables (age, gender, index date and family practice), all analyses were further adjusted for the main hypothesized confounding variables described above. In sensitivity analyses, prescriptions issued 12 months before the diagnosis were excluded from the analysis to reduce the risk of protopathic bias given that early presentations of FM might have been misdiagnosed and antibiotics prescribed.

Separate estimation models were conducted for the number of prescriptions compared to no prescriptions; the interval in years since the first ever prescription before the index date compared to no prescribing; the age group of the patients and the number of prescriptions; and antibiotic class (e.g. penicillins, sulfonamides, etc) with the risk of FM. We used the likelihood ratio test to assess potential temporal variation in the odds of FM after first antibiotic prescription. These tests were repeated for each class of antibiotics. Interaction between age at FM diagnosis and antibiotic prescribing was assessed by including interaction parameters between age at index date (<50, 50–64, 65–69, 80+) and antibiotic prescription (ever) using the likelihood ratio test to assess the strength of the evidence of age interaction (e.g. comparing models with and without the interaction parameters). Participants with missing data on any explanatory variables or covariates were excluded from the analyses (complete case analysis), which is valid if missingness is independent of the outcome (FM), conditional on all covariates (White & Carlin, 2010).

We performed additional sensitivity analysis to validate the findings from the complete-case analyses by using multiple imputations with chained equations (10 imputed data sets). Under the missing-at-random assumption, multiple imputations is superior to complete-case analysis (Sterne et al., 2009). As these analyses validated complete-case analysis, we are presenting the findings from multiple imputation in the main text (Findings for the complete-case analysis can be found in the Supplementary files, Figures S7–S10). Following Rothman (Rothman, 1990) and Ridker et al. (Ridker et al., 2008) the analyses did not adjust for multiple comparisons. Data were analysed using STATA version 15 (StataCorp, College Station, TX).

3 | RESULTS

Figure 1 shows a flow diagram of the sample identified in the CPRD database. Overall, 44,674 cases of FM and 133,513 matched controls were identified as meeting study entry criteria. The characteristics of these samples are shown in Table 1. Cases were more likely to have high BMI, be current or ex-smokers and have co-morbidities of diabetes, depression, insomnia and rheumatoid arthritis. They were also more likely to be taking immunosuppressant drugs, NSAIDs, statins, anti-hypertensive therapy and DMARDs. Excluding prescriptions issued in the year before diagnosis made little difference to these results as detailed in the Supplementary material (Figures S2–S6).

Figure 2 shows the odds ratios for the total number of antibiotic prescriptions across the study period, after adjusting for the listed co-variates. Patients were divided into quartiles in terms of the total number of prescriptions

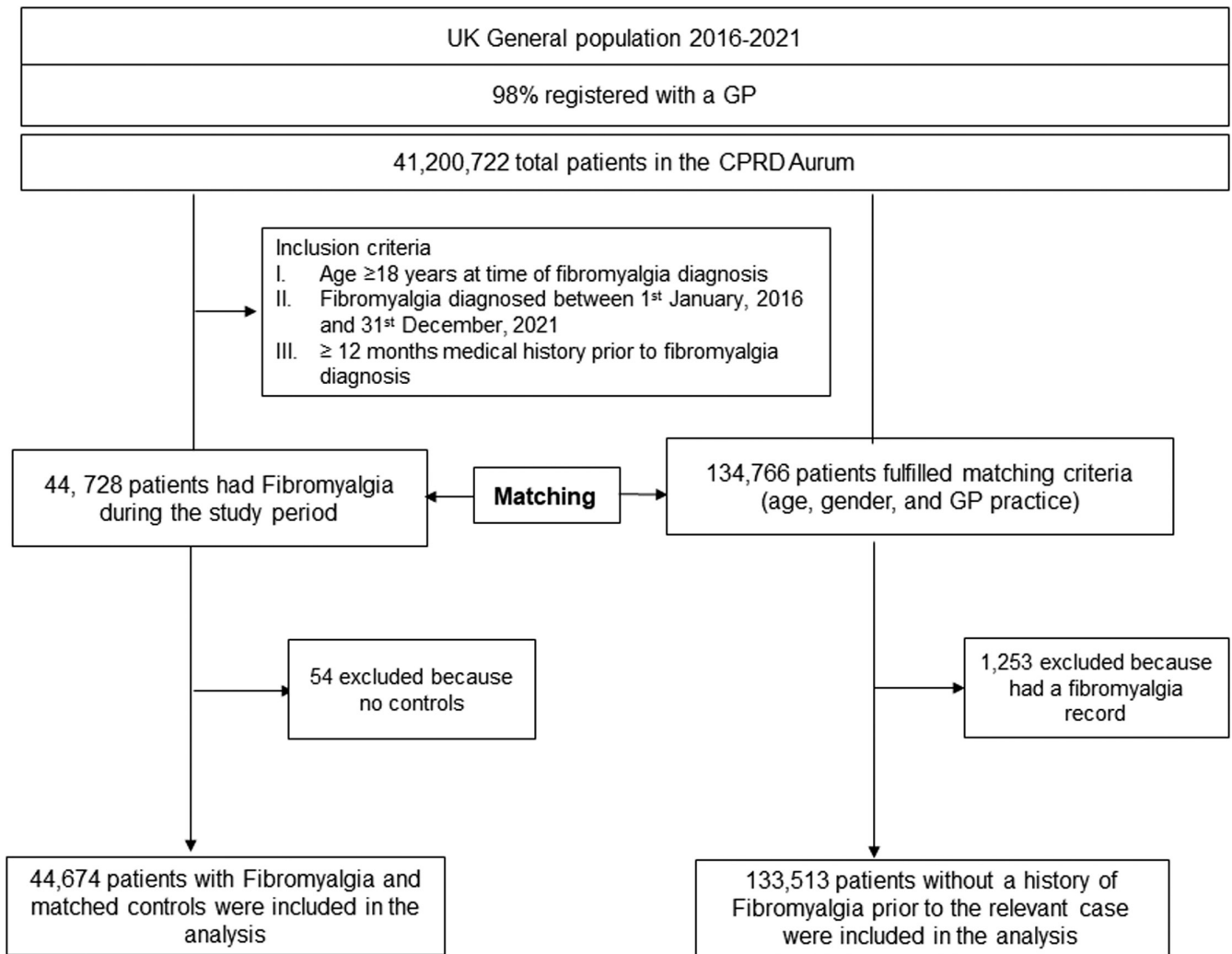


FIGURE 1 Flow diagram showing study participants.

received, indicating those with the largest number of prescriptions were more likely to receive an FM diagnosis. Figure 3 shows that the total time exposed to antibiotics, again divided into quartiles, was also associated with an FM diagnosis. Defining antibiotic prescribing as a continuous variable (Figure S1), we observed an overall 11% increment in the risk of fibromyalgia with each new antibiotic prescribing (adjusted relative risk=1.11, 95% CI, 1.08–1.14, $p < 0.001$).

Figures 4 and 5 show the effects of earliest and most recent recorded antibiotics. The odds ratios for the most recent antibiotic tend to overlap—except for an antibiotic in the most recent year. Overall, antibiotics increased the risk of fibromyalgia two-fold (adjusted odds ratios [aOR]=2.27, 95% confidence interval [CI]=2.10–2.44). The odds ratios for the earliest antibiotic, however, show a clear recency effect with antibiotics taken several years earlier showing no impact on the diagnosis of FM.

Finally, Figure 6 shows the effects of different antibiotics. All show an increased association with FM with

metronidazole (aOR=2.24, 95% CI 2.17–2.31) and tetracycline (aOR=2.7, 95% CI 2.01–2.13) having the largest effects.

Sensitivity analyses (Figures S2–S10) confirm the results of the main analyses, with only minor variations in the effect size.

4 | DISCUSSION

This study has shown an increased risk of FM following exposure to antibiotics. On the one hand, the association seemed strongest with the total number of prescriptions suggesting a dose–response effect; on the other hand, there seemed a marked recency effect with prescriptions issued closer to the diagnosis having the strongest association. The exception was prescriptions issued in the year immediately preceding diagnosis, but this may reflect a protopathic bias in which early FM symptoms were treated as infection related. Overall, these findings offer

TABLE 1 Sample characteristics.

	Cases, N = 44,674 (%)	Controls, N = 133,513 (%)
Gender—Female	40,455 (90)	120,788 (90)
Age—Mean (SD)	46 (13)	46 (13)
BMI		
Underweight	734 (2)	5684 (6)
Optimal	9796 (24)	39,777 (41)
Overweight	11,030 (27)	27,301 (27)
Obese	17,520 (44)	23,043 (24)
Missing	1037 (3)	2015 (2)
Smoking		
Never	15,725 (35)	55,853 (42)
Ex-smoker	6436 (14)	16,552 (12)
Current smoker	22,333 (50)	35,255 (26)
Missing	180 (1)	25,753 (19)
Ethnicity		
White	33,159 (74)	87,603 (66)
Black	971 (2)	3756 (3)
Asian	2259 (5)	8225 (6)
Mixed	749 (2)	2534 (2)
Other	4053 (9)	11,614 (9)
Missing	3483 (8)	19,781 (15)
Morbidities		
Diabetes	3697 (8)	6398 (5)
Insomnia	6176 (14)	5639 (4)
Neoplasm	2610 (6)	8226 (6)
Heart failure	196 (0)	1202 (1)
Myocardial infarction	400 (1)	1342 (1)
Peripheral artery disease	288 (1)	747 (1)
Chronic Kidney disease	2242 (5)	7060 (5)
Rheumatoid Arthritis	1651 (4)	1072 (1)
Lupus	438 (1)	238 (0)
Crohn's disease	454 (1)	437 (0)
Ulcerative colitis	386 (1)	502 (0)
Therapy		
Immunosuppressant drugs	1836 (4)	1700 (1)
NSAIDs	38,632 (86)	61,659 (46)
Corticosteroids	424 (1)	454 (0)
Statins	8256 (19)	16,772 (14)
Antihypertensive therapy	20,563 (48)	30,899 (25)
DMARDs	2951 (7)	1634 (1)

some support for the hypothesis that antibiotic exposure is implicated in the pathogenesis of FM. The mechanism through which that might occur, however, has not been directly studied. Nevertheless, as a number of recent studies have shown changes in the microbiome of patients with FM (Abomoelak et al., 2021; Clos-Garcia et al., 2019; Freidin et al., 2021; Minerbi et al., 2019) it seems plausible that antibiotics could have their effect through disrupting the 'healthy' microbiome. The close association between FM and irritable bowel syndrome, for example, would support a common aetiological pathway. There is preliminary evidence that faecal microbiome transplant might relieve symptoms of IBS (Johnsen et al., 2018) so given the known relationship between FM and IBS, the altered gut microbiome of the latter may also be implicated in the former.

The alternative explanation for these findings, as proposed by Ganjizadeh-Zavareh and colleagues (Ganjizadeh-Zavareh et al., 2019), is that antibiotic consumption may simply be a marker for recurrent infections and it is lowered immunity that precedes FM diagnosis. As FM presents some features in common with Lyme disease, an infectious origin has seemed possible. A number of studies have reported FM is more common following vaccination and infection with bacteria, such as mycoplasma, and viruses, such as hepatitis C, though this seems to be an association rather than a causal relationship (Cassisi et al., 2011). Yet in the present study, the fact that risk varies by the class of antibiotic (and presumably the range of susceptible organisms) might indicate that disruption of certain bacterial communities might be implicated rather than a more generic response to infection. Two of the antibiotics examined, for example, tetracycline and metronidazole, increased the chances of a subsequent diagnosis more than two-fold. The reported findings were also adjusted for variables that might relate to immune status (such as immunosuppressants) as well as some immune-related diseases.

The main strength of this study is the large number of patients involved, a figure exceeding most studies in the field. The main limitation of the study, as with any case-control design, is possible confounding which prevents assuming causality. Some potential confounders were addressed by adjusting for co-variables that could have influenced both prescribing and caseness, but residual confounding cannot be excluded. Adjusting for variables such as depression and insomnia that may be considered a part of the FM syndrome, might also indicate our reported effect sizes are conservative. The study relied on GPs making and recording the diagnosis of FM. Diagnosis may follow several years after initial presentation of symptoms

Cumulative volume of antibiotics

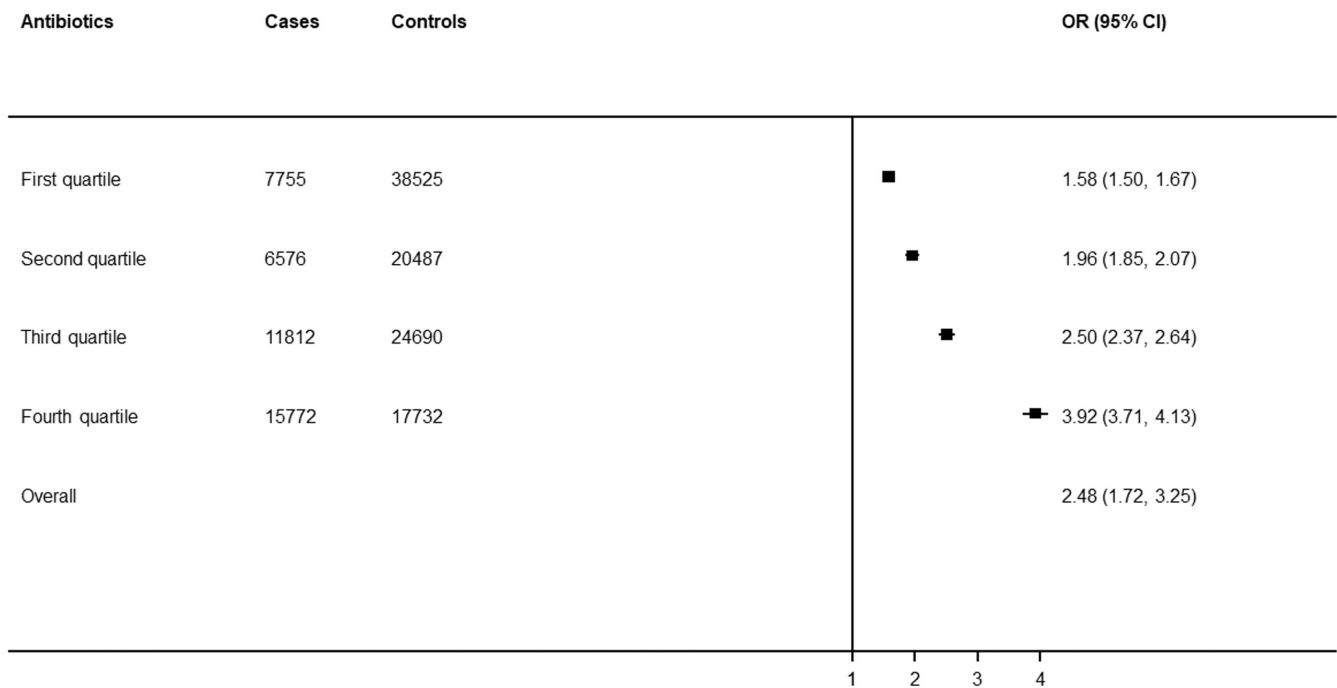


FIGURE 2 Total consumption of antibiotics (quartiles).

Cumulative exposure time to antibiotics

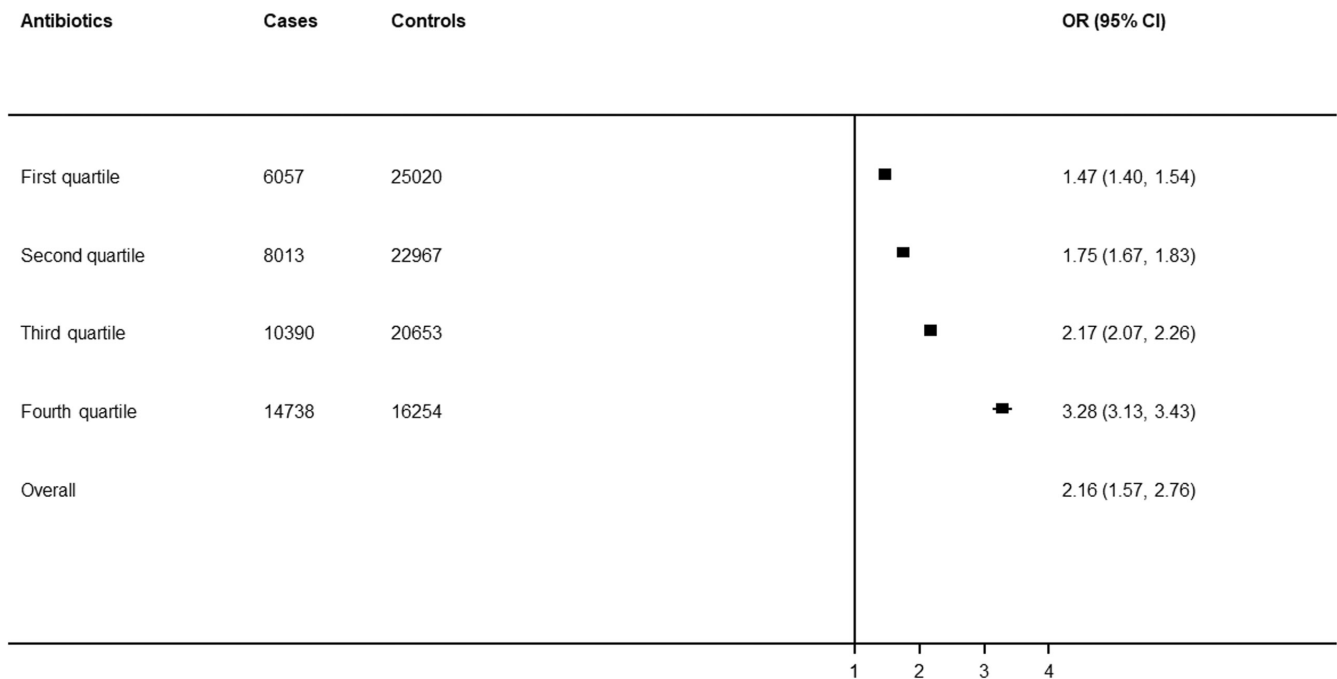


FIGURE 3 Total time exposed to antibiotics (quartiles).

(Gendelman et al., 2018) but antibiotics would be unlikely to be prescribed for earlier pain symptoms. Given that FM is mostly considered a diagnosis of exclusion (Qureshi

et al., 2021), it is possible that many of the controls also had FM, but again this provides a conservative bias to the results. The exposure variable of antibiotic prescriptions

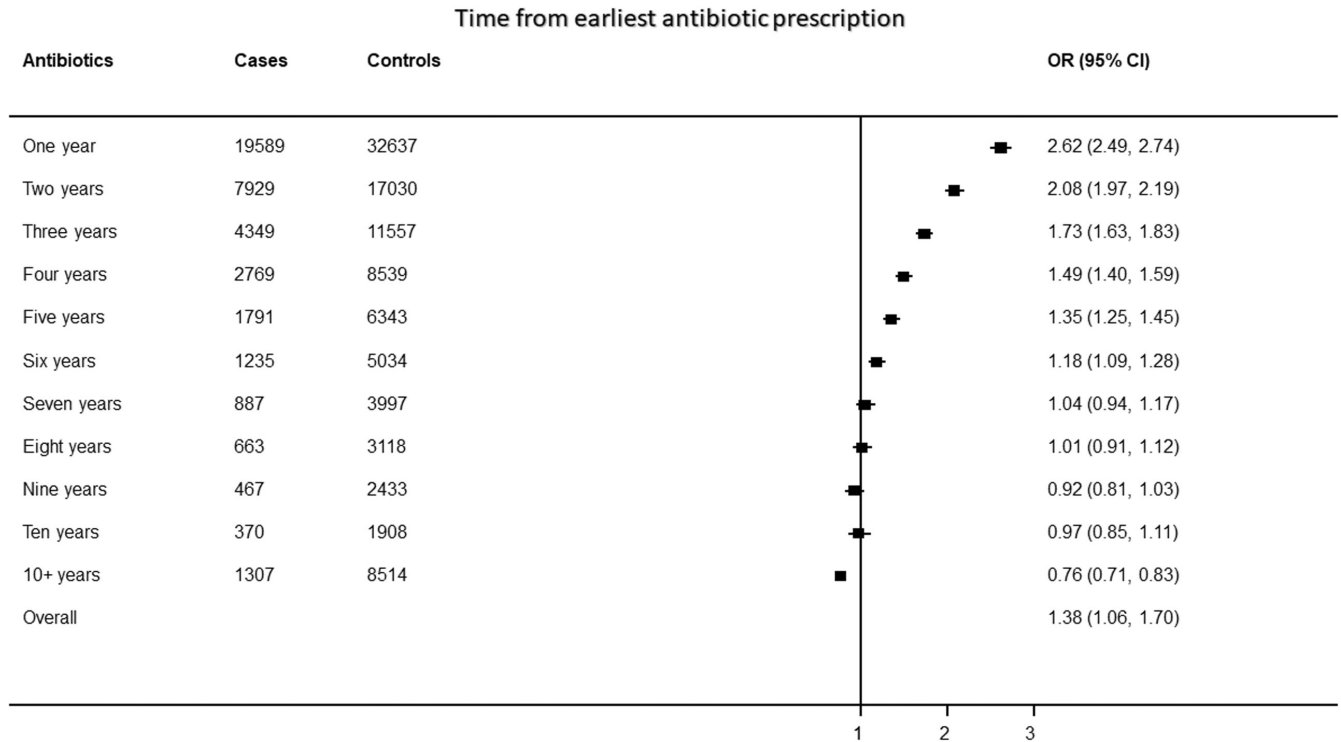


FIGURE 4 Time from the earliest recorded antibiotic.

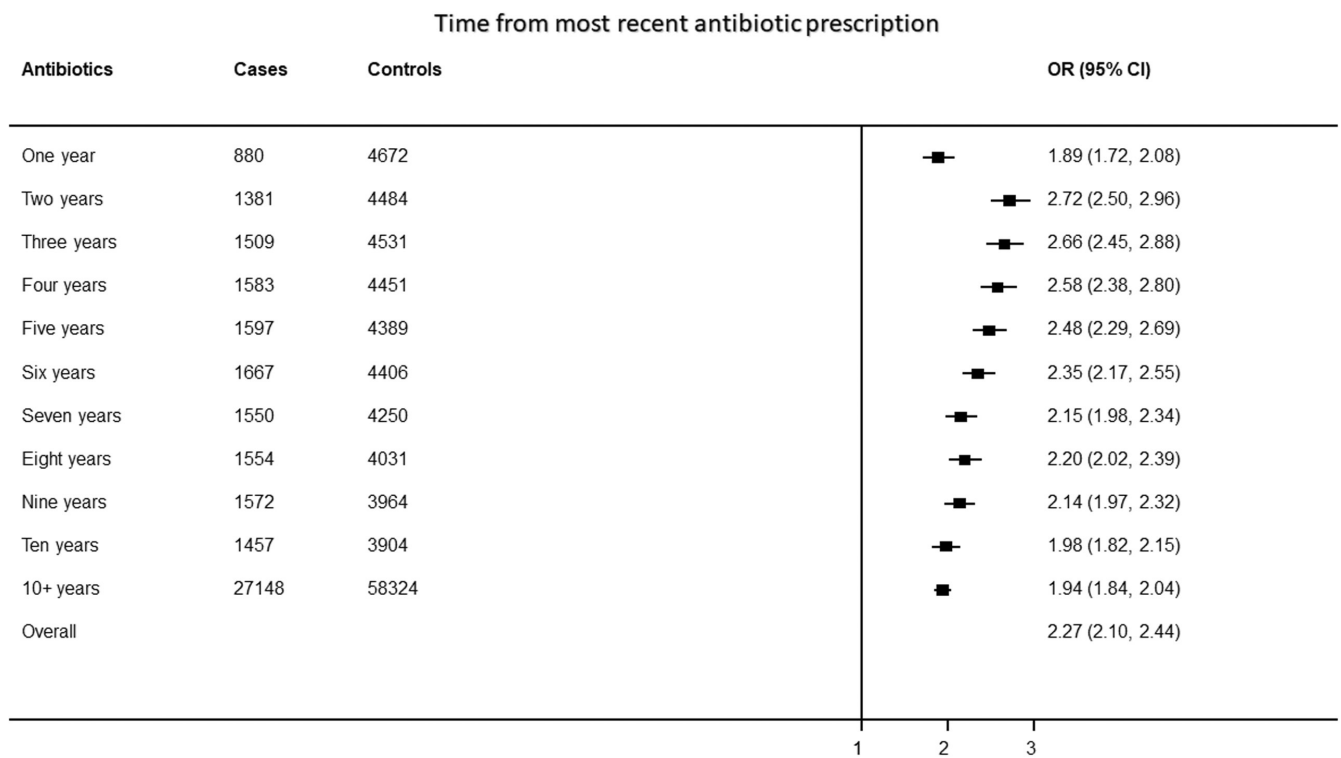


FIGURE 5 Time since most recent antibiotic.

is well recorded in primary care but does not include antibiotics prescribed in hospitals or outpatients. Hospital treatments, however, are generally of limited duration and

most antibiotic prescribing is primary care based. We have no evidence that prescriptions were taken to a pharmacist and the medication consumed, though non-adherence is

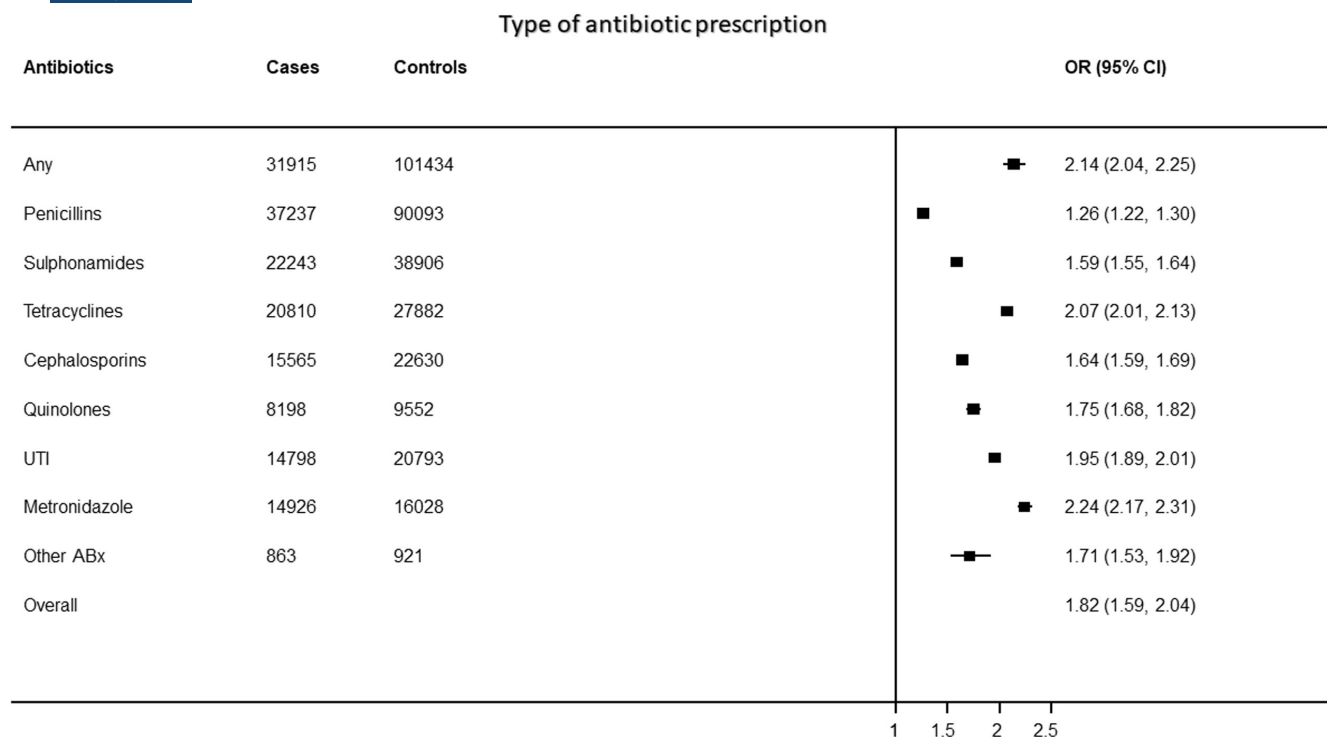


FIGURE 6 Effect of different antibiotics. All models fully adjusted models for neoplasm, MI, heart failure, PAD, CKD, RA, SLE, Crohn's disease, ulcerative colitis, diabetes, Immunosuppressants, corticosteroids, NSAIDs, smoking, BMI, ethnicity, and insomnia.

likely to be common to both cases and controls and unlikely to bias the observed estimates.

In a recent systematic review of the relationship between the gut microbiome and FM, Erdrich and colleagues argued that despite the plausibility of an association there was a paucity of good-quality evidence linking the two (Erdrich et al., 2020b). Nevertheless, the association between FM and IBS suggests that the gut-brain axis might be implicated in both with the microbiome playing a mediating role (Garofalo et al., 2023). While not directly measuring the microbiome, this study has shown a clear dose-response relationship between a known cause of dysbiosis, namely antibiotics and a diagnosis of fibromyalgia.

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CONFLICT OF INTEREST STATEMENT

No author reported any conflicts of interest.

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REFERENCES

- Abomoelak, B., Pemberton, V., Deb, C., Campion, S., Vinson, M., Mauck, J., Manipadam, J., Sudakaran, S., Patel, S., Saps, M., Enshasy, H. A. E., Varzakas, T., & Mehta, D. I. (2021). The gut microbiome alterations in pediatric patients with functional abdominal pain disorders. *Microorganisms*, 9, 2354.
- Alizadeh, N., Naderi, G., Kahrizi, M. S., Haghgouei, T., Mobed, A., & Shah-Abadi, M. E. (2023). Microbiota-pain association; recent discoveries and research progress. *Current Microbiology*, 80, 29.
- Armstrong, D., Ashworth, M., Dregan, A., & White, P. (2016). The relationship between prior antimicrobial prescription and meningitis: A case-control study. *The British Journal of General Practice*, 66, e228-e233.
- Bannerman, C. A., Douchant, K., Sheth, P. M., & Ghasemlou, N. (2021). The gut-brain axis and beyond: Microbiome control of spinal cord injury pain in humans and rodents. *Neurobiology of Pain*, 9, 100059.
- Binvignat, M., Sokol, H., Mariotti-Ferrandiz, E., Berenbaum, F., & Sellam, J. (2021). Osteoarthritis and gut microbiome. *Joint, Bone, Spine*, 88, 105203.
- Brenner, D., Cherry, P., Switzer, T., Butt, I., Stanton, C., Murphy, K., McNamara, B., Iohom, G., O'Mahony, S. M., & Shorten, G. (2021). Pain after upper limb surgery under peripheral nerve block is associated with gut microbiome composition and diversity. *Neurobiology of Pain*, 10, 100072.
- Brenner, D., Shorten, G. D., & O'Mahony, S. M. (2021). Postoperative pain and the gut microbiome. *Neurobiology of Pain*, 10, 100070.

- Cassisi, G., Sarzi-Puttini, P., & Cazzola, M. (2011). Chronic widespread pain and fibromyalgia: Could there be some relationship with infections and vaccinations? *Clinical and Experimental Rheumatology*, *29*, S118–S126.
- Clos-Garcia, M., Andrés-Marin, N., Fernández-Eulate, G., Abecia, L., Lavín, J. L., van Liempd, S., Cabrera, D., Royo, F., Valero, A., Errazquin, N., Vega, M. C. G., Govillard, L., Tackett, M. R., Tejada, G., González, E., Anguita, J., Bujanda, L., Orcasitas, A. M. C., Aransay, A. M., ... Falcón-Pérez, J. M. (2019). Gut microbiome and serum metabolome analyses identify molecular biomarkers and altered glutamate metabolism in fibromyalgia. *eBioMedicine*, *46*, 499–511.
- D'Onghia, M., Ciaffi, J., Lisi, L., Mancarella, L., Ricci, S., Stefanelli, N., Meliconi, R., & Ursini, F. (2021). Fibromyalgia and obesity: A comprehensive systematic review and meta-analysis. *Seminars in Arthritis and Rheumatism*, *51*, 409–424.
- Drago, L., Zuccotti, G. V., Romanò, C. L., Goswami, K., Villafaña, J. H., Mattina, R., & Parvizi, J. (2019). Oral–gut microbiota and arthritis: Is there an evidence-based axis? *Journal of Clinical Medicine*, *8*, 1753.
- Dregan, A., Charlton, J., Wolfe, C. D. A., Gulliford, M. C., & Markus, H. S. (2014). Is sodium valproate, an HDAC inhibitor, associated with reduced risk of stroke and myocardial infarction? A nested case–control study. *Pharmacoepidemiology and Drug Safety*, *23*, 759–767.
- Dregan, A., Matcham, F., Harber-Aschan, L., Rayner, L., Brailean, A., Davis, K., Hatch, S., Pariente, C., Armstrong, D., Stewart, R., & Hotopf, M. (2019). Common mental disorders within chronic inflammatory disorders: A primary care database prospective investigation. *Annals of the Rheumatic Diseases*, *78*, 688–695.
- Erdrich, S., Hawrelak, J. A., Myers, S. P., & Harnett, J. E. (2020a). A systematic review of the association between fibromyalgia and functional gastrointestinal disorders. *Therapeutic Advances in Gastroenterology*, *13*, 1–17.
- Erdrich, S., Hawrelak, J. A., Myers, S. P., & Harnett, J. E. (2020b). Determining the association between fibromyalgia, the gut microbiome and its biomarkers: A systematic review. *BMC Musculoskeletal Disorders*, *21*, 181.
- Freidin, M. B., Stalteri, M. A., Wells, P. M., Lachance, G., Baleanu, A.-F., Bowyer, R. C. E., Kurilshikov, A., Zhernakova, A., Steves, C. J., & Williams, F. M. K. (2021). An association between chronic widespread pain and the gut microbiome. *Rheumatology*, *60*, 3727–3737.
- Ganjizadeh-Zavareh, S., Sodhi, M., Spangehl, T., Carleton, B., & Etminan, M. (2019). Oral fluoroquinolones and risk of fibromyalgia. *British Journal of Clinical Pharmacology*, *85*, 236–239.
- Garofalo, C., Cristiani, C. M., Ilari, S., Passacatini, L. C., Malafoglia, V., Viglietto, G., Maiuolo, J., Oppedisano, F., Palma, E., Tomino, C., Raffaelli, W., Mollace, V., & Muscoli, C. (2023). Fibromyalgia and irritable bowel syndrome interaction: A possible role for gut microbiota and gut-brain Axis. *Biomedicine*, *11*, 1701.
- Gendelman, O., Amital, H., Bar-On, Y., Ben-Ami Shor, D., Amital, D., Tiosano, S., Shalev, V., Chodick, G., & Weitzman, D. (2018). Time to diagnosis of fibromyalgia and factors associated with delayed diagnosis in primary care. *Best Practice & Research. Clinical Rheumatology*, *32*, 489–499.
- Gill, H., Perez, C. D., Gill, B., El-Halabi, S., Lee, Y., Lipsitz, O., Park, C., Mansur, R. B., Rodrigues, N. B., McIntyre, R. S., & Rosenblat, J. D. (2021). The prevalence of suicidal behaviour in fibromyalgia patients. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *108*, 110078.
- Herrett, E., Gallagher, A. M., Bhaskaran, K., Forbes, H., Mathur, R., van Staa, T., & Smeeth, L. (2015). Data resource profile: Clinical practice research datalink (CPRD). *International Journal of Epidemiology*, *44*, 827–836.
- Johnsen, P. H., Hilpüsch, F., Cavanagh, J. P., Leikanger, I. S., Kolstad, C., Valle, P. C., & Goll, R. (2018). Faecal microbiota transplantation versus placebo for moderate-to-severe irritable bowel syndrome: A double-blind, randomised, placebo-controlled, parallel-group, single-centre trial. *The Lancet Gastroenterology & Hepatology*, *3*, 17–24.
- Liu, L., Wu, Q., Chen, Y., Ren, H., Zhang, Q., Yang, H., Zhang, W., Ding, T., Wang, S., Zhang, Y., Liu, Y., & Sun, J. (2023). Gut microbiota in chronic pain: Novel insights into mechanisms and promising therapeutic strategies. *International Immunopharmacology*, *115*, 109685.
- Minerbi, A., Gonzalez, E., Brereton, N., Fitzcharles, M.-A., Chevalier, S., & Shir, Y. (2023). Altered serum bile acid profile in fibromyalgia is associated with specific gut microbiome changes and symptom severity. *Pain*, *164*, e66–e76.
- Minerbi, A., Gonzalez, E., Brereton, N. J. B., Anjarkouchian, A., Dewar, K., Fitzcharles, M.-A., Chevalier, S., & Shir, Y. (2019). Altered microbiome composition in individuals with fibromyalgia. *Pain*, *160*, 2589–2602.
- Minerbi, A., & Shen, S. (2022). Gut microbiome in anesthesiology and pain medicine. *Anesthesiology*, *137*, 93–108.
- Pappolla, M. A., Manchikanti, L., Candido, K. D., Grieg, N., Seffinger, M., Ahmed, F., Fang, X., Andersen, C., & Trescot, A. M. (2021). Insulin resistance is associated with central pain in patients with fibromyalgia. *Pain Physician*, *24*, 175–184.
- Qureshi, A. G., Jha, S. K., Iskander, J., Avanthika, C., Jhaveri, S., Patel, V. H., Rasagna Potini, B., & Talha Azam, A. (2021). Diagnostic challenges and management of fibromyalgia. *Cureus*, *13*, e18692.
- Ridker, P. M., Danielson, E., Fonseca, F. A. H., Genest, J., Gotto, A. M., Kastelein, J. J. P., Koenig, W., Libby, P., Lorenzatti, A. J., MacFadyen, J. G., Nordestgaard, B. G., Shepherd, J., Willerson, J. T., & Glynn, R. J. (2008). Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *The New England Journal of Medicine*, *359*, 2195–2207.
- Rothman, K. J. (1990). No adjustments are needed for multiple comparisons. *Epidemiology*, *1*, 43–46.
- Salliss, M. E., Farland, L. V., Mahner, N. D., & Herbst-Kralovetz, M. M. (2021). The role of gut and genital microbiota and the estrobolome in endometriosis, infertility and chronic pelvic pain. *Human Reproduction Update*, *28*, 92–131.
- Sánchez Romero, E. A., Meléndez Oliva, E., Alonso Pérez, J. L., Martín Pérez, S., Turróni, S., Marchese, L., & Villafaña, J. H. (2021). Relationship between the gut microbiome and osteoarthritis pain: Review of the literature. *Nutrients*, *13*, 716.
- Sterne, J. A. C., White, I. R., Carlin, J. B., Spratt, M., Royston, P., Kenwood, M. G., Wood, A. M., & Carpenter, J. R. (2009). Multiple imputation for missing data in epidemiological and clinical research: Potential and pitfalls. *BMJ*, *338*, b2393.
- White, I. R., & Carlin, J. B. (2010). Bias and efficiency of multiple imputation compared with complete-case analysis for missing covariate values. *Statistics in Medicine*, *29*, 2920–2931.

- Wolf, A., Dedman, D., Campbell, J., Booth, H., Lunn, D., Chapman, J., & Myles, P. (2019). Data resource profile: Clinical practice research datalink (CPRD) aurum. *International Journal of Epidemiology*, *48*, 827–836.
- Zetterman, T., Markkula, R., & Kalso, E. (2021). Glucose tolerance in fibromyalgia. *Medicine (Baltimore)*, *100*, e27803.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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