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Fluoroquinolone antibiotics and type 2 diabetes mellitus

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ABSTRACT

Exposure to fluoroquinolone antibiotics is postulated as a risk factor for subsequent development of type 2 diabetes. It is hypothesized that fluoroquinolones induce an intracellular magnesium deficit that can lead to insulin resistance. A temporal correlation is reported between the rate of outpatient prescription of quinolones and the incidence of diabetes during the period 1980–2011 with a lag of approximately two years ($R^2 = 0.86$, $P < 10^{-9}$). The increase in incidence of diabetes after 1990 and the recent decrease in the number of new cases are both reflected in the fluoroquinolone prescription rates. A geographical correlation is reported (adj. $R^2 = 0.7$, $P < 0.0001$) between rates of increase in prevalence of diabetes in each U.S. state and a model using only local rates of outpatient fluoroquinolone prescription, local rates of increase in the prevalence of obesity, and local rates of population growth as predictor variables. Prescription rates of non-quinolone antibiotics correlated less well with the local rates of increase in prevalence of diabetes. The data are consistent with fluoroquinolone exposure predisposing an individual to develop diabetes with a probability that strongly depends upon factors that also lead to an increase in obesity. According to the hypothesis, much of the increase in the incidence of type 2 diabetes in the U.S. from 1990 to the present can be attributed to fluoroquinolone exposure.

Type 2 diabetes mellitus was once considered a "Western disease" but has now developed into a public health crisis of global proportions [1]. In the United States the prevalence of type 2 diabetes has been climbing since about 1990 at such a rate that the disease currently affects almost 8% of the population [2]. Much has been written about the link between the rising rates of obesity (defined as BMI > 30 kg/m^2) and type 2 diabetes, but the prevalence of diabetes is increasing in the non-obese population as well. The present article examines a possible risk factor in the development of diabetes that has not previously received attention and that may affect both the obese and the non-obese: the use of fluoroquinolone antibiotics.

Since the publication of maps showing the rates of outpatient prescription of antibiotics in each American state [3] there has been speculation as to reasons for the apparent geographical correlation between high rates of antibiotic prescription and an elevated risk for illnesses such as cardiovascular disease, stroke, and diabetes [4]. One possible explanation for the (possibly artifactual) connection is that antibiotics deplete beneficial gut bacteria [5]. Another (possibly complementary) explanation is proposed here.

Hypothesis

It is postulated that drugs that chelate multivalent metal ions and can penetrate cell membranes induce an intracellular magnesium deficiency that increases the probability of development of insulin resistance. This can lead (when accompanied by other risk factors) to type 2 diabetes. Further, it is suggested that fluoroquinolone antibiotics pose a particularly high risk of such a chain of events, and that they are responsible for much of the increase in the prevalence of type 2 diabetes in the United States from 1990 to the present day.

Magnesium deficiency has been linked with type 2 diabetes in numerous studies [6]. It has been suggested that low magnesium intake may be a risk factor for development of diabetes [7] and conversely that supplementation with magnesium may reduce the risk of developing diabetes [8]. Magnesium deficiency has been shown to exacerbate insulin resistance and compromise glucose homeostasis in people already afflicted with type 2 diabetes [9]. The biochemical basis for the effect of intracellular magnesium deficiency on the signaling pathways involved in insulin resistance is not fully understood, but it is likely to involve suppression of activity of enzymes requiring magnesium as a cofactor, such as tyrosine kinase [10].

Further supporting the hypothesis, there are indications that complications of diabetes such as retinopathy and hypertension

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may be worsened or even caused by magnesium deficiency [11]. Magnesium deficiency has been implicated in gestational diabetes and its complications [12]. In addition to magnesium, other multivalent metal ions may affect biochemical processes involved in the development of insulin resistance and thus of type 2 diabetes. Increased levels of transition metals (including vanadium, chromium, manganese, cobalt, molybdenum and nickel) have been linked with improved hyperglycemia [13].

Fluoroquinolones are broad-spectrum antibiotics derived from nalidixic acid that inhibit bacterial topoisomerases. Although very effective therapeutically, fluoroquinolones have been linked with serious side effects such as tendinopathy [14], peripheral neuropathy [15], retinopathy [16], renal failure [17], hypertension [18], and seizures [19]. These effects can be rationalized as resulting from a drug-induced magnesium deficiency [20], and according to the hypothesis it is not coincidental that they resemble the complications resulting from type 2 and gestational diabetes. There has, moreover, been a history of dysglycemia associated with certain fluoroquinolone antibiotics. Gatifloxacin was withdrawn from clinical use after reports of drug-induced hyperglycemia [21] and other fluoroquinolones have been reported to interfere with glucose homeostasis [22].

The precise mechanism by which fluoroquinolones might induce intracellular magnesium deficiency is unclear. It may involve the metal-chelating properties of the 3-carboxyquinolone substructure that is common to all fluoroquinolone antibiotics [23] and the fact that the 6-fluoro substituent on the pharmacophore gives rise to sufficient lipophilicity that the drugs can dissolve in and penetrate cell membranes [24]. It has been suggested that intracellular fluoroquinolones may exist almost exclusively as the magnesium complex [23]. Diffusion or active transport of such a complex into the extracellular environment would lead to depletion of intracellular magnesium – a process that may be stoichiometric or catalytic and would be only very slowly reversible, if at all [25]. Thus, the effects of fluoroquinolones on intracellular magnesium levels might be considered to be almost cumulative (and it is noteworthy that the side-effects of fluoroquinolone therapy may manifest or persist many months after treatment) [15]. Alternatively, it is perhaps possible that fluoroquinolones could affect magnesium metabolism by disruption of renal reaborption of this electrolyte.

It might be objected that a typical course of fluoroquinolone antibiotics is quite short (on the order of a few days), and that the half-life of the drugs in the human body is only a few hours. The amount ingested, however, is large. A typical human body contains about 1 mol of magnesium, of which about half is located in bone and about 1% in extracellular fluid. A daily dose of 1 g of ciprofloxacin (molecular weight 331.3) is about 3 mmol. During a 10-day course, a patient will ingest an amount of the drug equivalent to 3% of total body magnesium, 6% of magnesium not located in bone, or 300% of magnesium located in extracellular fluid.

Evaluation of the hypothesis

The incidence of diabetes per 1000 in the non-institutionalized U.S. population aged 18–79 during the period 1980–2011 [26] is shown in Fig. 1(A). Five distinct periods, I–V, may be distinguished. During period I (1980–1991) diabetes incidence was fairly stable at about 3.5/1000. It rose during period II (1991–1994) to about 4.5/1000 and remained at about this level during period III (1994–1997). During period IV (1997–2009) diabetes incidence rose dramatically to a peak of almost 9/1000 after which, during period V (2009–present), it began to decline.

Fig. 1(B) shows estimated rates of outpatient prescriptions of fluoroquinolone antibiotics during 1980–2010 [3,27,28]. The data from Ref. [28] underestimate fluoroquinolone prescriptions rela-

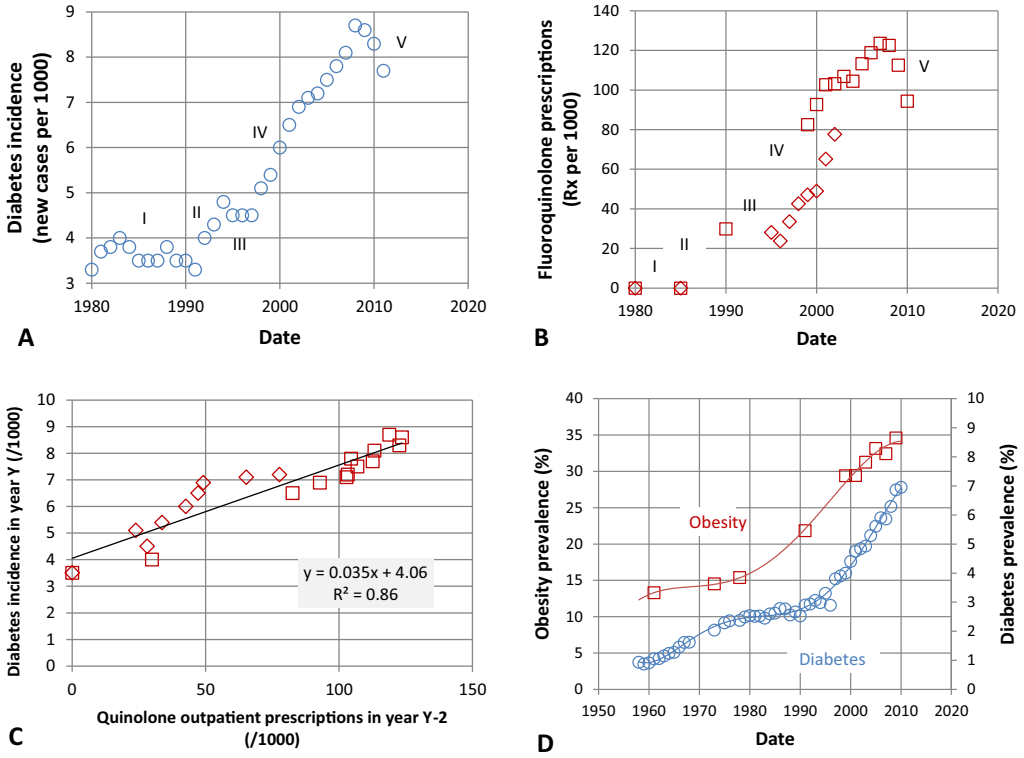

Fig. 1. (A) Incidence of diabetes in the non-institutionalized U. S. population aged 18–79. (B) U.S. national outpatient prescription rates of fluoroquinolone antibiotics from Refs. [3] and [27] (squares) and [28] (diamonds). (C) Correlation between incidence of diabetes in a given year and outpatient fluoroquinolone prescription rate 2 years previously. (D) Prevalence of diabetes in the whole U.S. population plotted with prevalence of obesity.

tive to data from Ref. [3] for the 4 years in which the two sources overlap (1999–2002) by a factor of about 1.5. Notwithstanding this discrepancy, it is still possible to distinguish the same five periods noted above for the incidence of diabetes in the fluoroquinolone prescription data, the fluoroquinolone data leading the diabetes data by about 2 years. Prior to 1986 there were no FDA-approved fluoroquinolones available in the U.S. (period I). Beginning with norfloxacin (approved in 1986), followed by ciprofloxacin (1987) and ofloxacin (1990), among others, a first generation of fluoroquinolones was introduced (period II), prescriptions of which reached an approximately steady state by the early 1990s (period III). Starting with the approval of levofloxacin (1996), a second generation of fluoroquinolones was introduced, the other notable drug being moxifloxacin (1999). A period of growth in fluoroquinolone prescriptions ensued (period IV), culminating in 2007 when levofloxacin became the most-prescribed of all fluoroquinolones. Following the imposition of a "black box" warning by the FDA on the drug class in 2008, however, prescriptions of fluoroquinolones began to decline (period V).

Fig. 1(C) shows the correlation between diabetes incidence in a given year with the outpatient fluoroquinolone prescription rate (uncorrected for the offset between data sources for fluoroquinolone prescription rates noted above) 2 years previously ($R^2 = 0.86$, $P < 10^{-9}$). The correlation is even better when data from the two sources are normalized ($R^2 = 0.93$, $P < 10^{-9}$). The probability of developing diabetes following a fluoroquinolone prescription is thus estimated at about 3.5 percent.

Attempting to make causal inferences from ecological data is of course fraught with difficulty. Other factors that have been implicated in the increase in the incidence of diabetes have also increased during the period 1980–2010: for example, obesity and factors that may lead to an increase in obesity, such as changes in diet or increasing physical inactivity. There have also been other drug classes introduced during this period, notably proton pump inhibitors (which may cause magnesium deficiency) and SSRIs. However, such factors, if posited as alternatives to the fluoroquinolones, must explain not only the increase in the incidence of diabetes but also the detailed form that the increase actually took, as well as the recent *decrease* in the number of new cases. SSRI prescriptions declined in 2004–5, [29] long before the decrease in incidence of diabetes, while proton pump inhibitors are not known to cause problems with glucose metabolism (indeed, their use has been suggested as a treatment for diabetes) [30].

The evolution of the prevalence of diabetes in the entire U.S. population from years 1958 to 2010 is shown in Fig. 1(D), [2] together with the parallel evolution of obesity [31]. The prevalence of obesity begins to accelerate in about 1980 (i.e., preceding the change in the prevalence of diabetes by about 10–12 years) but shows a less rapid acceleration than that in the prevalence of diabetes. The prevalence of obesity increased by a factor of only about 2.2 between 1980 and 2010, whereas the prevalence of diabetes increased by a significantly larger factor (about 2.8 between 1990 and 2010). Thus it seems unlikely that obesity alone can explain the increase in prevalence of diabetes after 1990, although, as discussed in detail below, factors leading to an increase in obesity are certainly involved in the phenomenon.

The hypothesis that fluoroquinolone use may lead to type 2 diabetes was explored further by examining correlations between local rates of increase in the prevalence of diabetes and obesity together with local rates of prescription of antibiotics in different states in the USA. Data for the prevalence of obesity and diabetes were obtained from the BRFSS survey of American states [32] in which prevalence of obesity and diabetes, and the proportion of diabetics who are obese (among much other data) have been recorded for the population over the age of 18 for the years 1994–present. The incidence data for diabetes are unfortunately sparser and more noisy than the prevalence data when considered state-by-state, and are available only from 1996 to 2010. Therefore it was not possible at the state level to perform the type of simple linear regression with fluoroquinolone outpatient prescription rates described above for national US data.

From the BRFSS data the rates of increase in prevalence of diabetes and obesity were obtained for each state i, giving excellent linear fits (R^2 0.86 and 0.95, respectively, averaged across all 50 states). These rates were considered together with data from the CDDEP survey [3] in which outpatient prescription rates of each class of antibiotic were reported for each state for the period 1999–2010.

A simple model was used to justify the use of diabetes prevalence data, rather than incidence data, for each state. The difference between prevalence of diabetes in year y and year $y-1$ (ΔD) was assumed to be related to the incidence of diabetes in that year, $d(y)$, the mortality rate of diabetics in that year, $m(y)$, and the prevalence of diabetes in the previous year, $D(y-1)$, as follows:

$$\begin{aligned}\Delta D &= D(y) - D(y-1)\\ &= \frac{D(y-1)P(y-1) + d(y)P(y) - m(y)P(y)}{P(y)} - D(y-1)\\ &= -\frac{\Delta P}{P(y)}D(y-1) + d(y) - m(y) \qquad (1)\end{aligned}$$

where $P(y)$ is the population in year y and $\Delta P = P(y) - P(y-1)$. Thus, a correlation was sought between the rate of increase of prevalence of diabetes in each state i (D_i'), the population growth rate in that state (P_i'), the relative diabetic mortality rate in that state m_i, estimated by dividing the mortality rate from diabetes in 2010 [33] by the prevalence of diabetes in 2010 in that state, [34] and the risk factors considered here for the incidence of diabetes in that state, namely: (a) the average rate of outpatient fluoroquinolone prescription and (b) measures related to the prevalence of obesity: the average prevalence of obesity (O_i) and the rate of increase in the prevalence of obesity from 1994 to 2010 (O_i').

Table 1 shows the correlations (Pearson r, correlations with $P > 0.05$ are shown as zero) between (a) the local rate of increase in prevalence of diabetes (D_i') and outpatient prescription rates of different classes of antibiotic in each state in the period 1999–2008, [35] (b) outpatient prescription rates of each class of antibiotic with each other, and (c) the local rate of increase in prevalence

Table 1
Cross-correlations between D_i', O_i', and prescription rates of various classes of antibiotics in 50 U.S. states (excluding District of Columbia).

	D_i'	Quinolones	Cephalosporins	Macrolides	Other	Penicillins	O_i'
Quinolones	0.65						0.50
Cephalosporins	0.63	0.73					0.67
Macrolides	0.60	0.87	0.82				0.59
Other	0.43	0.52	0.72	0.53			0.44
Penicillins	0.40	0.80	0.63	0.80	0.49		0.36
Tetracyclines	0	0	0.39	0.40	0.35	0.53	0
All non-Quinolones	0.57						0.58
O_i'	0.77						

Table 2
Correlations between D_i' and various measures of the prevalence of obesity in 50 U.S. states (excluding the District of Columbia).

	Pearson r
O_i (averaged 1994–2010)	0.69
O_i (averaged 1994–1997)	0.44
O_i (averaged 1998–2001)	0.60
O_i (averaged 2002–2005)	0.66
O_i (averaged 2005–2010)	0.72
O_i'	0.77

Table 3
F-ratios for multiple linear regression with D_i' as the response variable and O_i', Q_i', and A_i' as predictor variables.

	O_i'	Q_i	A_i
Cephalosporins	29.7	9.2	0.092
Macrolides	39.7	10.0	1.7
All non-quinolones	42.5	13.0	2.9

of obesity (O_i') and outpatient prescription rates of different classes of antibiotic.

A slightly better correlation is obtained between D_i' and average outpatient prescription rates for quinolones in years 1999–2008 than for any other class of antibiotic; however, examination of the cross-correlations reveals that there appear to be two significant, independent predictor variables: the outpatient prescription rates of quinolones and the rate of increase in prevalence of obesity, as discussed in more detail below.

Table 2 shows the correlation between D_i' and the two measures of obesity described above (in all cases, $P < 0.01$). A better correlation is obtained between D_i' and the rate of change in the prevalence of obesity than between D_i' and the prevalence of obesity itself averaged over the complete period of 1994–2010. The correlation between D_i' and the prevalence of obesity increases with the time at which the prevalence of obesity is measured, also suggesting that the risk factor in developing diabetes is not obesity *per se*, but rather a factor that leads to an *increase* in obesity, examples being the *per capita* intake of food, nutritional content of food, physical inactivity, etc.

Fig. 2 shows the correlations between D_i' and O_i' and between D_i' and Q_i (the local average rate of outpatient prescription of quinolones 1999–2008). The regression line of D_i' versus Q_i goes through the origin; i.e., the rate of increase in prevalence of diabetes in this fit is zero when the rate of outpatient prescription of fluoroquinolones is zero.

Multiple linear regression using a standard least-squares protocol was performed with D_i' as the response variable and three predictor variables: O_i', Q_i, and the local rate of outpatient prescription of a second, non-quinolone antibiotic (A_i). ANOVA F–ratios are shown in Table 3 for various choices of the second antibiotic (residuals exhibited a normal distribution). The simplest model that fits the D_i' data is therefore shown to require only the rate of outpatient prescription of fluoroquinolones and the rate of increase in the prevalence of obesity as predictor variables.

Fig. 3(B) shows the results of a least-squares regression of D_i' versus O_i', Q_i and the local population growth rate P_i' [36]. No statistically significant correlation was found with m_i calculated as described above. The model has adjusted R^2 of 0.70 ($P < 0.0001$). Fig. 3(A, C–E) shows the geographical distribution of D_i', O_i', Q_i and that of the fit. The details of the model are shown in Table 4.

In this geographical analysis the possibility of reverse causation must be considered: i.e., fluoroquinolone prescriptions may be more common in diabetics than in the general population. There are two reasons to doubt this in the present context: firstly, the average diabetic population across the 50 states is fairly low (6.4%) with a standard deviation of 1%, while the standard deviation of outpatient fluoroquinolone prescription rates is about 12%. It is unlikely that a 1% variation in the diabetic population could induce a 12% change in prescription rates. Secondly, the observed correlation is not with the prevalence of diabetes but with the *rate of change* of that prevalence.

The picture that is suggested by the two analyses presented above is that the incidence of type 2 diabetes would not have risen in the period 1990–2010 had the fluoroquinolones not been introduced, but that factors leading to an increase in obesity greatly influence the probability of developing type 2 diabetes following exposure to a fluoroquinolone. This was examined further by consideration of the local rates of increase in prevalence of *non-obese* diabetics (ND_i'). This could be done using data in the BRFSS survey reporting the proportion of diabetics who are obese for the period 1995–present (although since the population is not static there will be some errors in this approach). The geographical distribution of the rate of increase in prevalence of non-obese diabetics in all 50 states is shown in Fig. 4(A). It is evident that a large swath in the mid-West, corresponding to the Great Lakes region and the flood plains of the Missouri and Mississippi rivers, displays low or zero increases in nonobese diabetes. There are also relatively low levels in the "four-corners" states with the exception of Arizona and in northern New England.

Since it is hypothesized that that fluoroquinolone-mediated magnesium depletion might account for the increase in diabetes, correlations between ND_i' and local mineral concentrations in surface water and soil were examined (this data is available for certain elements at a county level from the National Geochemical Survey [37]; state data were obtained from within-state population-averaged county-level data). Significant correlations were obtained

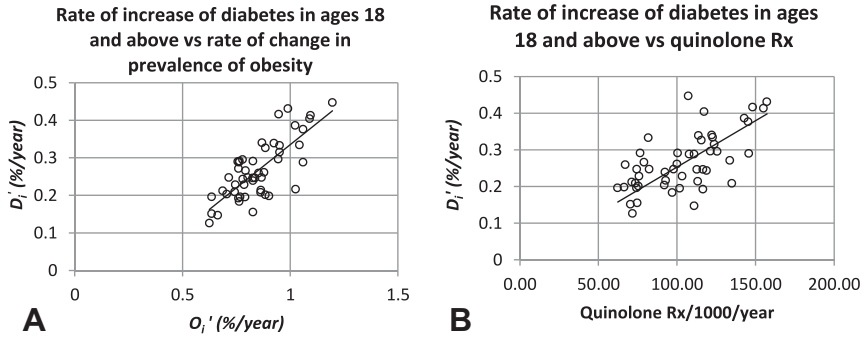

Fig. 2. Correlation between the rate of increase of the prevalence of diabetes in ages 18+ in each state with (A) the rate of increase in obesity and (B) the rate of outpatient prescription of fluoroquinolone antibiotics.

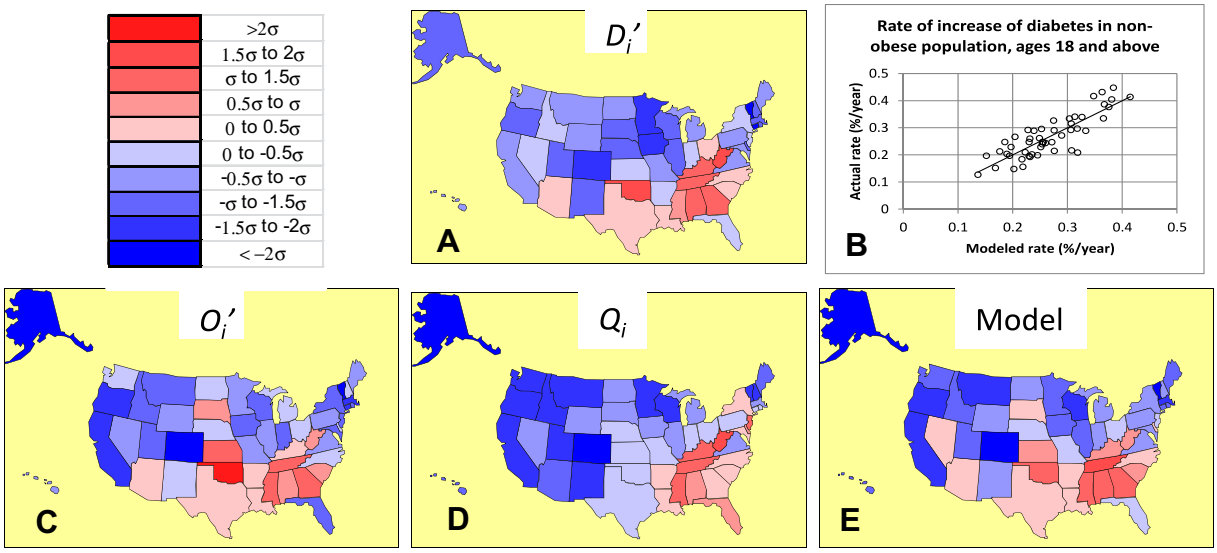

Fig. 3. (B) Modeled rate of increase in diabetes versus actual for 50 US states; geographical distributions of deviations from the mean of: (A) rates of increase in prevalence of diabetes; (C) rates of increase in prevalence of obesity 1994–2010; (D) average rates of outpatient prescription of quinolones 1999–2008; (E) modeled rate of increase in diabetes as described in Table 4.

Table 4
Details of fit for multiple linear regression with D_i' as the response variable and O_i', Q_i', and P_i' as predictor variables.

	Mean (σ)	Model coefficient	Std. error	*t* Ratio	*F* ratio
Intercept		−0.166	0.042	−3.97	
O_i' (%/year)	0.85 (0.065)	0.335	0.055	6.05	36.54
Q_i (R_x/1000/year)	104 (13)	0.00123	0.00029	4.33	18.72
P_i' (%/year/10)	0.098 (0.036)	0.213	0.089	2.38	5.69

only with magnesium ($r = -0.32$; $P = 0.03$) and marginally with selenium ($r = -0.27$; $P = 0.06$). Less significant correlations were obtained with sodium ($P = 0.07$), aluminum ($P = 0.14$), calcium, zinc, copper, titanium, phosphorus, iron and manganese (all $P > 0.2$).

A standard least-squares multiple linear regression analysis was performed with ND_i' as the response variable and O_i', Q_i and P_i' as predictor variables, giving an adjusted R^2 of 0.42 ($P < 0.0001$). The results of the model are shown in Table 5 and in Fig. 4(D).

Because of the correlation with magnesium concentrations in surface water and soil noted above, the local water hardness [38] was included in the model as an additional predictor variable. This added marginally to the goodness of fit (adjusted R^2 of 0.45, $P < 0.0001$) but the effect of water hardness was barely statistically significant (probability > $|t|$ = 0.052). The details of this fit are summarized in Table 6.

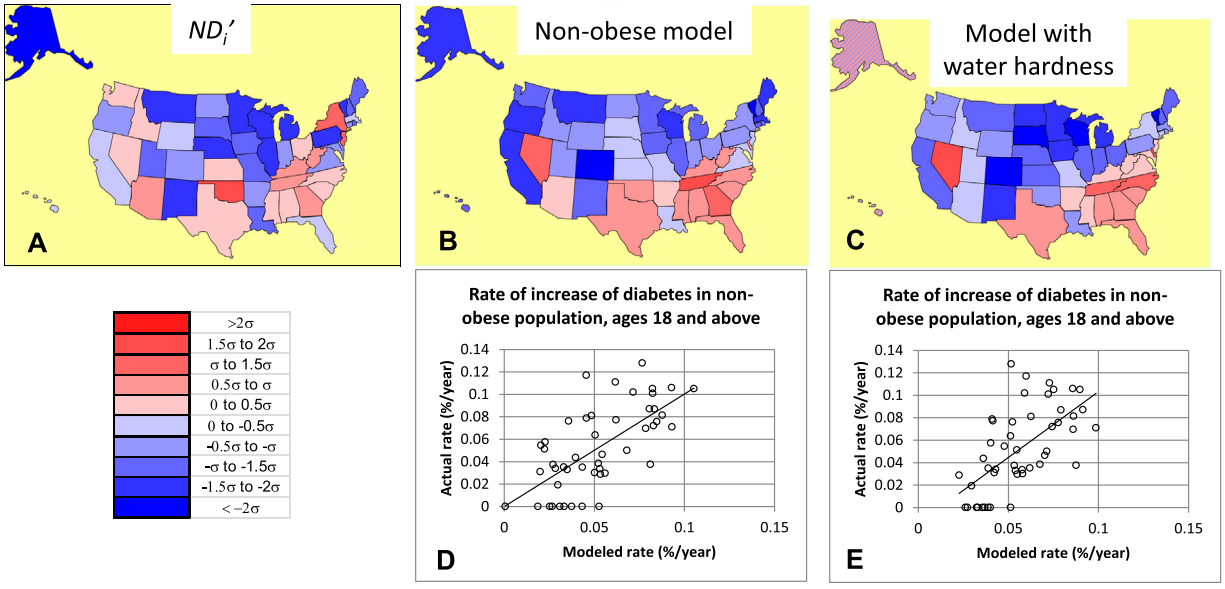

Fig. 4. Geographical distribution of deviations from the mean of: (A) the rate of increase in the prevalence of non-obese diabetics; (B) modeled rate of increase in prevalence of non-obese diabetics as summarized in Table 5; (C) modeled rate of increase in prevalence of non-obese diabetics including local water hardness as a predictor variable, as summarized in Table 6 (excluding Alaska and Hawaii); (D, E) Actual versus modeled rates of increase in the prevalence of non-obese diabetics using models summarized in Tables 5 and 6.

Table 5
Details of fit for multiple linear regression with ND_i' as the response variable and O_i', Q_i and P_i' as predictor variables.

	Mean (σ)	Model coefficient	Std. error	*t* Ratio	*F* ratio
Intercept		−0.096	0.029	−3.37	
O_i' (%/year)	0.85 (0.065)	0.072	0.037	1.97	3.89
Q_i (R_x/1000/year)	104 (13)	0.00065	0.00019	3.46	11.95
P_i' (%/year/10)	0.098 (0.036)	0.189	0.059	3.21	10.33

Table 6
Details of fit for multiple linear regression with D_i' as the response variable and O_i', Q_i and P_i' as predictor variables.

	Mean (σ)	Model coefficient	Std. error	*t* Ratio	*F* ratio
Intercept		−0.085	0.028	−3.03	
O_i' (%/year)	0.85 (0.065)	0.087	0.036	2.41	5.81
Q_i (R_x/1000/year)	104 (13)	0.00054	0.00019	2.82	7.93
P_i' (%/year/10)	0.098 (0.036)	0.196	0.057	3.45	11.87
Water hardness (ppm)	107 (35)	−0.000119	$5.97 \cdot 10^{-5}$	−2.0	3.99

Discussion

The hypothesis that fluoroquinolones can cause type 2 diabetes has been tested using two independent ecological correlations. The fact that each measure supports the hypothesis reduces the uncertainty inherent in ecological studies. Geographical correlations were also noted between the local rate of increase in the prevalence of obesity and the local rate of increase in the prevalence of diabetes, including in the non-obese. The latter result is consistent with a factor other than obesity, but correlated with the rate of change in obesity, being responsible for an increase in the probability of development of diabetes following fluoroquinolone exposure. Finally, in the non-obese, there are indications that higher environmental concentrations of magnesium (and, possibly, selenium) may be protective against development of diabetes.

The results presented here, while suggestive, do not conclusively prove a connection between the ingestion of fluoroquinolone antibiotics and the development of type 2 diabetes. Follow-up longitudinal studies should be undertaken to examine the history of individual diabetic patients for previous fluoroquinolone exposure. In addition, the possible connection between fluoroquinolones and diabetes could be probed in a more direct, mechanistic way. The proposed metal ion chelation mechanism could be tested by analysis of urine of patients undergoing fluoroquinolone therapy.

If the fluoroquinolone/diabetes link is borne out by further investigation, the implications are considerable. Diabetes might conceivably be treated by far more aggressive magnesium supplementation than has so far been attempted. Fluoroquinolones are potent antibiotics but their use would ideally be restricted to the treatment of serious infections. Fluoroquinolones could perhaps be rendered safer by co-administration with metal salts (especially magnesium salts) in doses timed so as not to limit the availability of the drug.

Conflicts of interest

None declared.

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References

[1] Hu F. Globalization of diabetes: the role of diet, lifestyle, and genes. Diabetes Care 2011;34:1249–57.
[2] "*Long-term trends in diagnosed diabetes*", published online by the Centers for Disease Control and Prevention at <http://www.cdc.gov/diabetes/statistics/slides/long_term_trends.pdf>; 2013 [accessed 05.08.13].
[3] Published online by the Center for Disease Dynamics, Economics and Policy at <http://cddep.org/resistancemap/use/all#.Uf_P1aywWQI>; 2013 [accessed 05.08.13].
[4] See, for example, <www.wired.com/wiredscience/2011/11/antibiotic-use-connection>; 2013 [accessed 05.08.13].
[5] Blaser M. Antibiotic overuse: Stop the killing of beneficial bacteria. Nature 2011;476:393–4.
[6] Nadler J. Disorders of magnesium metabolism. Endocrinol Metab Clin N Am 1995;24:623–41;
Schnack Ch, Bauer I, Pregant P, Hopmeier P, Schernthaner G. Hypomagnesaemia in type 2 (non-insulin-dependent) diabetes mellitus is not corrected by improvement of long-term metabolic control. Diabetologia 1992;35:77–9;
Paolisso G, Sgambato S, Giugliano D, et al. Impaired insulin-induced erythrocyte magnesium accumulation is correlated to impaired insulin-mediated glucose disposal in type 2 (non-insulin-dependent) diabetic patients. Diabetologia 1988;31:910–5;
Sjögren A, Floren C, Nilsson A. Magnesium, potassium and zinc deficiency in subjects with type II diabetes mellitus. Acta Med Scand 1988;224:461–5;
Barbagallo M, Dominquez L, Galioto A, et al. Role of magnesium in insulin action, diabetes and cardio-metabolic syndrome X. Mol Aspects Med 2003;24:39–52.
[7] Colditz G, Manson J, Meir J, Rosner B, Willett W, Speizer F. Diet and risk of clinical diabetes in women. Am J Clin Nutr 1992;55:1018–23;
Humphries S, Kushner H, Falkner B. Low dietary magnesium is associated with insulin resistance in a sample of young, nondiabetic black Americans. Am J Hypertens 1999;12:747–56.
[8] He K, Liu K, Davighis M, et al. Magnesium intake and incidence of metabolic syndrome among young adults. Circulation 2006;113:1675–82;
Dong J, Xun P, He K, Qin L. Magnesium intake and risk of type 2 diabetes: meta-analysis of prospective cohort studies. Diabetes Care 2011;34:2116–22.
[9] Durlach J, Rayssiguier Y. Données nouvelles sur les relations entre magnésium et hydrates de carbone. Magnesium 1983;2:192–224.
[10] Takaya J, Higashino H, Kobayashi Y. Intracellular magnesium and insulin resistance. Magnes Res 2004;17:126–36.
[11] Nadler J, Buchanan T, Natarajan R, Antonipillai I, Bergman R, Rude R. Magnesium deficiency produces insulin resistance and increased thromboxane synthesis. Hypertension 1993;21:1024–9;
McNair P, Christiansen C, Madsbad S, et al. Hypomagnesaemia, a risk factor in diabetic retinopathy. Diabetes 1978;27:1075–7.
[12] Bardicef M, Bardicef O, Sorokin Y, Altura B, Cotton D, Resnick L. Extracellular and intracellular magnesium depletion in pregnancy and gestational diabetes. Am J Obstet Gynaecol 1995;172:1009–13.
[13] Thompson K, Chiles J, Yuen V, Tse J, McNeill J, Orvig C. Comparison of anti-hyperglycemic effect amongst vanadium, molybdenum, and other metal maltol complexes. J Inorg Biochem 2004;90:683–90;
Walter R, Uriu-Hare J, Olin K, et al. Copper, zinc, manganese and magnesium status and complications of diabetes mellitus. Diabetes Care 1991;14:1050–6.
[14] Mehlhorn A, Brown D. Safety concerns with fluoroquinolones. Ann Pharmacother 2007;41:1859–66.
[15] Cohen J. Peripheral neuropathy associated with fluoroquinolones. Ann Pharmacother 2001;35:1540–7.
[16] Gelatt K, van der Woerdt A, Ketring K, et al. Enrofloxacin-associated retinal degeneration in cats. Vet Ophthalmol 2001;4:99–106;
Etminan M, Forooghian F, Brophy J, Bird S, Maberley D. Oral fluoroquinolones and the risk of retinal detachment. JAMA 2012;307:1414–9.
[17] Bird S, Etminan M, Brophy J, Hartzema A, Delaney J. Risk of acute kidney injury associated with the use of fluoroquinolones. C.M.A.J. 2013;185:E475–82.
[18] See, for example, <http://www.ehealthme.com/ds/levaquin/hypertension>; 2013 [accessed 05.08.13].
[19] Kushner J, Peckman H, Snyder C. Seizures associated with fluoroquinolones. Ann Pharmacother 2001;35:1194–8.
[20] Pfister K, Mazur D, Vormann J, Stahlmann R. Diminished ciprofloxacin-induced chondrotoxicity by supplementation with magnesium and vitamin E in immature rats. Antimicrob Agents Chemother 2007;51:1022–7;
Stahlmann R, Förster C, Shakibaei M, Vormann J, Günther T, Merker H. Magnesium deficiency induces joint cartilage lesions in juvenile rats which are identical to quinolone-induced arthropathy. Antimicrob Agents Chemother 1995;39:2013–8;
Hall M, Finnoff J, Smith J. Musculo-skeletal complications of fluoroquinolones. Clin Rev Curr Concepts 2011;3:132–42Fulop T. Hypomagnesemia. <http://emedicine.medscape.com/article/2038394-overview#a0101>; 2013 [accessed 05.08.13].
[21] Park-Wyllie L, Juurlink D, Kopp A, et al. Outpatient gatifloxacin therapy and dysglycemia in older adults. N Eng J Med 2006;354:1352–61.
[22] Aspinall S, Good C, Jiang R, McCarren M, Dong D, Cunningham F. Severe dysglycemia with the fluoroquinolones: a class effect? Clin Infect Dis 2009;49:402–8.

[23] Lecomte S, Baron M, Chenon M, Coupry C, Moreau N. Effect of magnesium complexation by fluoroquinolones on their antibacterial properties. Antimicrob Agents Chemother 1994;38:2810–6.
[24] Bensikaddour H, Fa N, Burton I, et al. Characterization of the interactions between fluoroquinolone antibiotics and lipids: a multitechnique approach. Biophys J 2008;94:3035–46.
[25] Jahnen-Dechent W, Ketteler M. Magnesium basics. Clin Kidney J 2012;5(Suppl. 1):i3–i14. doi: 10.1093/ndtplus/sfr163.
[26] "Crude and Age-Adjusted Incidence of Diagnosed Diabetes per 1,000 Population Aged 18–79 Years, United States, 1980–2011", Centers for Disease Control and Prevention (CDC), National Center for Health Statistics, Division of Health Interview Statistics, data from the National Health Interview Survey, published online at <http://www.cdc.gov/diabetes/statistics/incidence/fig2.htm>; 2013 [accessed 05.08.13]. These data are 3-year moving averages, except for 2011, which is a 2-year moving average.
[27] Ciprofloxacin prescriptions for 1990 from, Sahm D, Petersen D, Critchley I, Thornsberry C. Analysis of ciprofloxacin activity against *Streptococcus pneumoniae* after 10 years of use in the United States. Antimicrob Agents Chemother 2000;44:2521–4.
[28] Linder J, Huang E, Steinman M, Gonzales R, Stafford R. Fluoroquinolone prescribing in the United States: 1995 to 2002. Am J Med 2005;118:259–68.
[29] Gibbons R, Brown C, Hur K, et al. Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. Am J Psychiatry 2007;164:1356–63.
[30] Mefford I, Wade E. Proton pump inhibitors as a treatment method for type II diabetes. Med Hypotheses 2009;73:29–32.
[31] Data from NHES survey (1963-70), first, second, and third NHANES surveys (NHANES I, 1971-1974; NHANES II, 1976-1980; and NHANES III, 1988-1994) and National Center for Health Statistics: National Health and Nutrition Examination Survey (1999-2010).
[32] The Behavioral Risk Factor Surveillance System: see <http://www.cdc.gov/brfss/> and <http://www.apps.nccd.cdc.gov/DDTSTRS/default.aspx#div5> for state-specific data; 2013 [accessed 05.08.13].
[33] The Centers for Disease Control and Prevention (CDC), National Center for Health Statistics, Division of Vital Statistics, National Vital Statistics Report Volume 61, Number 4, Table 19, May 8, 2013.
[34] This approach has a number of problems: it neglects mortality of diabetics from causes other than diabetes, and assumes that the mortality rate of diabetics is not changing. In fact, it appears to be decreasing: see Gregg E, Cheng Y, Saydah S, et al., Trends in death rates among U.S. adults with and without diabetes between 1997 and 2006. Diabetes Care 2012; 35: 1252–1257. In the statistical analysis that follows this factor is not significant.
[35] Very similar fits were obtained with the complete data set from 1999–2010. The truncation was used here because (1) the basic model described with reference to Fig. 1 assumes a delay between fluoroquinolone prescription and the diagnosis of diabetes; and (2) there was a decline in fluoroquinolone prescription rates beginning in 2009 following the "black box" warnings concerning tendon ruptures with fluoroquinolone treatment.
[36] Data from Table 1: "Intercensal estimates of the resident population for the United States, regions, states, and Puerto Rico: April 1, 2000 to July 1, 2010" (ST-EST00INT-01), U.S. Census Bureau, Population Division, release date: September 2011.
[37] Data were obtained from the USGS National Geochemical Survey database: <http://mrdata.usgs.gov/geochem/>; 2013 [accessed 05.08.13].
[38] Data (as ppm equivalent mass of CaCO3) from E. K. Lohr, S. K. Love, "The industrial utility of public water supplied in the United States, 1952", USGS Water Supply Papers 1299 and 1300 (1954).