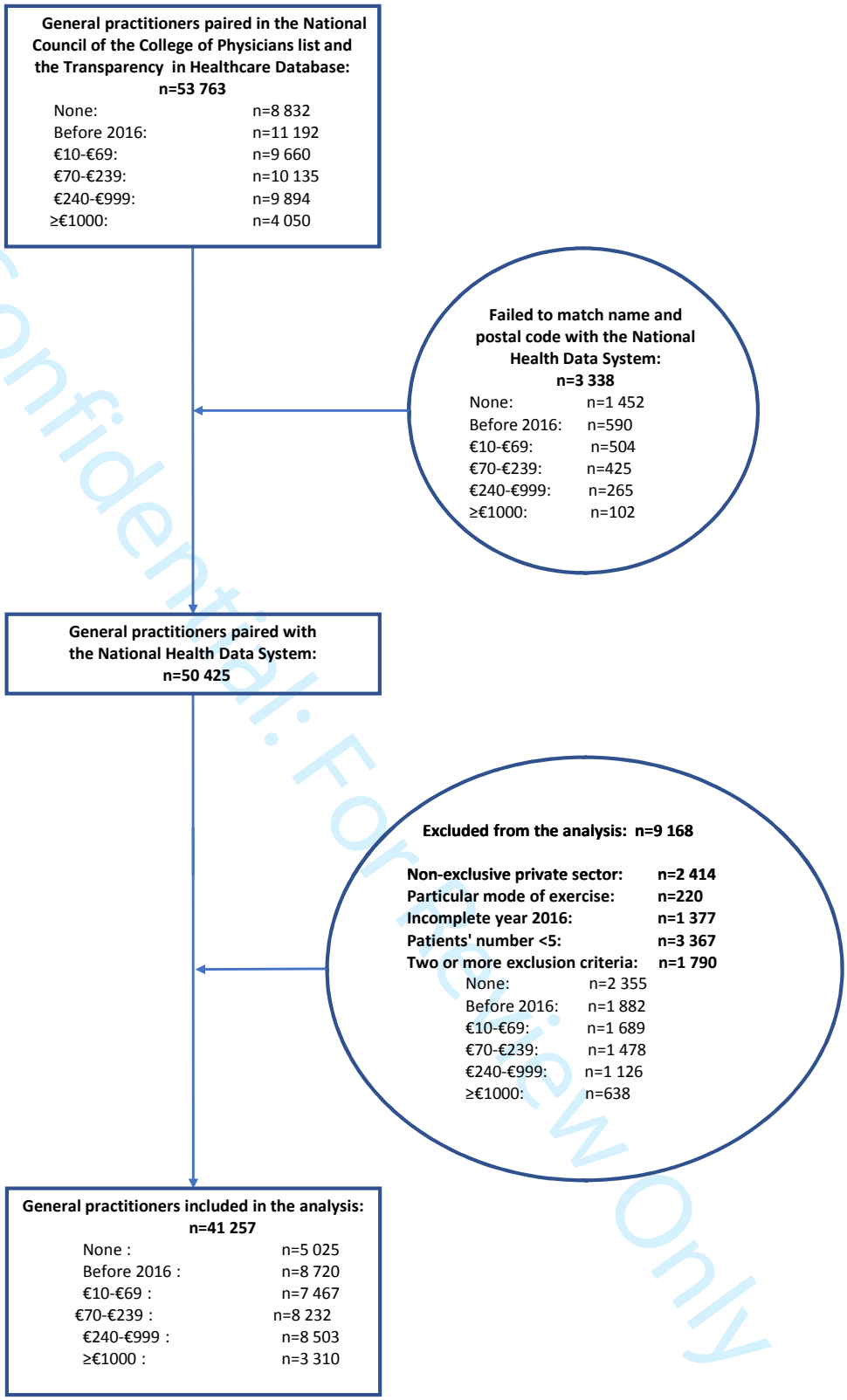
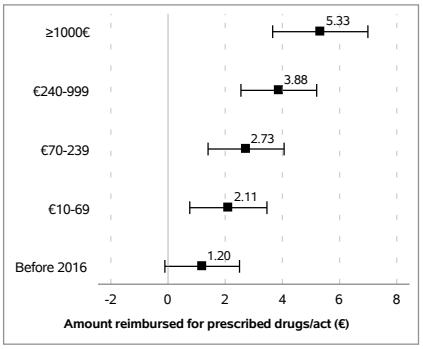
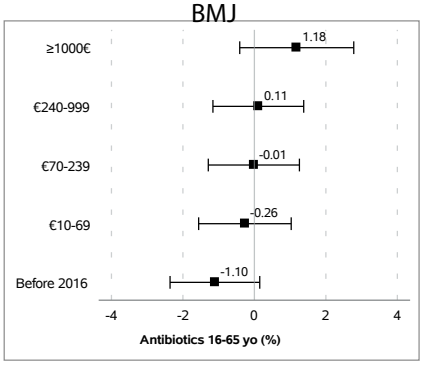
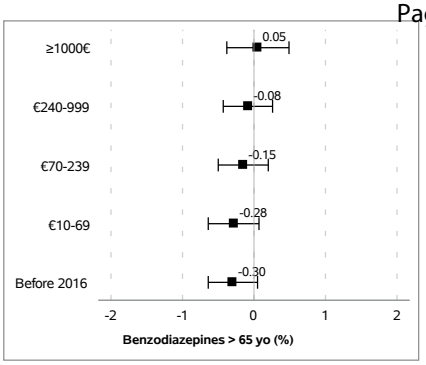
Association between benefits paid by pharmaceutical companies to French general practitioners and their drug prescriptions in 2016: a retrospective study using the French Transparency in Healthcare and National Health Data System databases

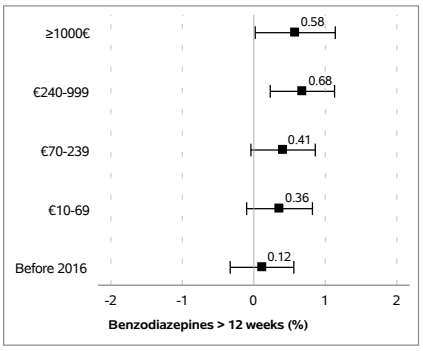
Journal:	*BMJ*
Manuscript ID	BMJ-2019-050887
Article Type:	Research
BMJ Journal:	BMJ
Date Submitted by the Author:	28-May-2019
Complete List of Authors:	Goupil, Bruno; Department of General Medicine, University Rennes 1 BALUSSON, Frédéric; EA 7449 (Pharmacoepidemiology and Health Services Research) REPERES, Univ Rennes, Rennes University Hospital Naudet, Florian; Univ Rennes, CHU Rennes, Inserm, CIC 1414 [(Centre d'Investigation Clinique de Rennes)]; Rennes 1 University, Department of Adult Psychiatry, Rennes University Hospital Esvan, Maxime; Univ Rennes, CHU Rennes, Inserm, CIC 1414 [(Centre d'Investigation Clinique de Rennes)] Bastian, Benjamin; Department of General Medicine, University Rennes 1 Chapron, Anthony; Department of General Medicine, University Rennes 1; Univ Rennes, CHU Rennes, Inserm, CIC 1414 [(Centre d'Investigation Clinique de Rennes)] Frouard, Pierre; Department of General Medicine, University Rennes 1
Keywords:	database, conflict of interests, drug prescription, influence, general practitioner, pharmaceutical industry, physician payment sunshine act, benefits

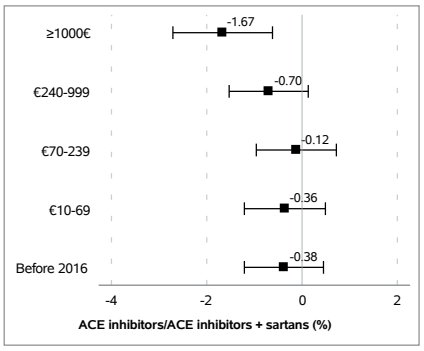


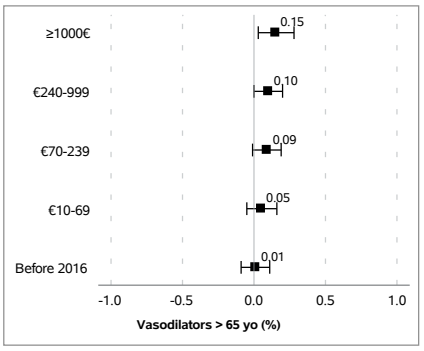

≥1000€
€240-999
€70-239
€10-69
Before 2016
5.33
3.88
2.73
2.11
1.20
-2 0 2 4 6 8
Amount reimbursed for prescribed drugs/act (€)

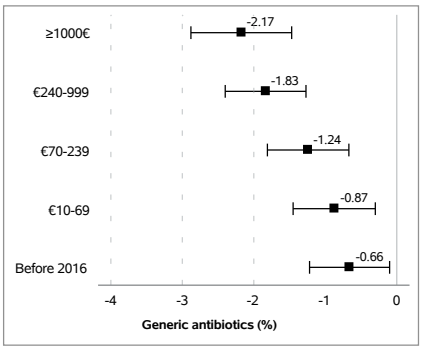

≥1000€
€240-999
€70-239
€10-69
Before 2016
1.18
0.11
-0.01
-0.26
-1.10
-4 -2 0 2 4
Antibiotics 16-65 yo (%)

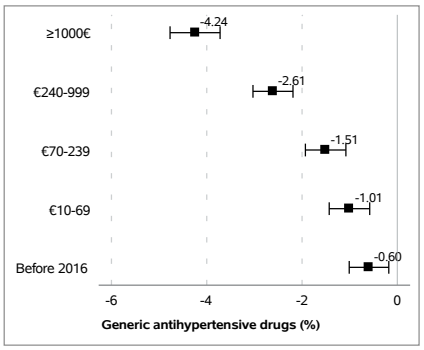

≥1000€
€240-999
€70-239
€10-69
Before 2016
0.05
-0.08
-0.15
-0.28
-0.30
-2 -1 0 1 2
Benzodiazepines > 65 yo (%)

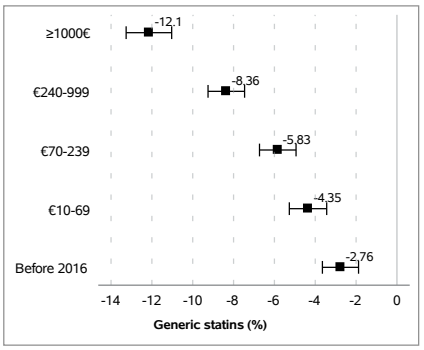

≥1000€
€240-999
€70-239
€10-69
Before 2016
0.58
0.68
0.41
0.36
0.12
-2 -1 0 1 2
Benzodiazepines > 12 weeks (%)


≥1000€
€240-999
€70-239
€10-69
Before 2016
-1.67
-0.70
-0.12
-0.36
-0.38
-4 -2 0 2
ACE inhibitors/ACE inhibitors + sartans (%)


≥1000€
€240-999
€70-239
€10-69
Before 2016
0.15
0.10
0.09
0.05
0.01
-1.0 -0.5 0.0 0.5 1.0
Vasodilators > 65 yo (%)


≥1000€
€240-999
€70-239
€10-69
Before 2016
-2.17
-1.83
-1.24
-0.87
-0.66
-4 -3 -2 -1 0
Generic antibiotics (%)


≥1000€
€240-999
€70-239
€10-69
Before 2016
-4.24
-2.61
-1.51
-1.01
-0.60
-6 -4 -2 0
Generic antihypertensive drugs (%)


≥1000€
€240-999
€70-239
€10-69
Before 2016
-12.1
-8.36
-5.83
-4.35
-2.76
-14 -12 -10 -8 -6 -4 -2 0
Generic statins (%)

OUTCOME	None	Before 2016	€10-€69	€70-€239	€240-€999	≥€1000	All	Univariate p value	Multivariate p value
Amount reimbursed for drug prescriptions/act (€) ¤	45.8 ± 40.1	47.8 ± 24.4	48.2 ± 21.8	49.4 ± 21.5	51.5 ± 22	53.2 ± 21	49.1 ± 25.3	**<0.001**	**<0.001**
Anti-platelet aggregation drugs (%)	87.3 ± 10.8	86.9 ± 9.2	87.2 ± 9.1	87.1 ± 8	86.8 ± 7.3	86.7 ± 6.9	87 ± 8.6	0.006	0.004
Antibiotics 16-65 yo (%) ¤	35.6 ± 30	35.8 ± 23	36.8 ± 24.9	37.3 ± 21	38.1 ± 19.1	41 ± 21.9	37.2 ± 23.2	**<0.001**	**<0.001**
Benzodiazepines > 65 yo (%) ¤¤	9.7 ± 7.9	9.5 ± 5.9	9.5 ± 5.9	9.6 ± 5.7	9.7 ± 5	10 ± 5	9.6 ± 5.9	**<0.001**	**<0.001**
Benzodiazepines >12 weeks (%) ¤¤	14 ± 9.3	14.2 ± 7.8	14.4 ± 8.1	14.6 ± 7.7	14.8 ± 6.9	14.8 ± 6.5	14.5 ± 7.7	**<0.001**	**<0.001**
ACE inhibitor/ACE inhibitors + sartans (%) ¤¤	44.3 ± 17.1	44 ± 14.9	44.2 ± 14.2	44.7 ± 13.4	43.9 ± 12.4	42.9 ± 12.7	44.1 ± 14.1	**<0.001**	**<0.001**
Vasodilators > 65 yo (%) ¤¤	0.8 ± 1.8	0.8 ± 1.6	0.8 ± 1.6	0.8 ± 1.6	0.9 ± 1.9	1 ± 1.8	0.8 ± 1.7	**<0.001**	**<0.001**
Generic antibiotics (%) ¤¤	87.3 ± 10.8	86.6 ± 9.7	86.5 ± 9.4	86.1 ± 9.2	85.5 ± 8.9	85.1 ± 8.9	86.2 ± 9.5	**<0.001**	**<0.001**
Generic antidepressants (%) ¤¤¤	91.3 ± 10.5	91.4 ± 8.9	91.4 ± 8.7	91.3 ± 7.8	91.3 ± 7.2	90.9 ± 7.2	91.3 ± 8.4	0.162	0.184
Generic antihypertensive drugs (%) ¤¤	84.7 ± 8.2	84.1 ± 7.3	83.7 ± 7.1	83.2 ± 6.6	82.1 ± 6.3	80.3 ± 7	83.2 ± 7.1	**<0.001**	**<0.001**
Generic PPIs (%) ¤¤	99.9 ± 0.9	99.9 ± 0.8	99.9 ± 0.8	99.9 ± 0.5	99.9 ± 0.8	99.9 ± 0.4	99.9 ± 0.7	0.025	0.028
Generic statins (%) ¤¤¤	77.6 ± 16.3	74.8 ± 15.4	73.2 ± 15.5	71.9 ± 14.2	69.2 ± 13.7	65.3 ± 14	72.3 ± 15.2	**<0.001**	**<0.001**

Appendix 1

Physicians and patients' characteristics

GROUP	None n= 5 025	Before 2016 n= 8 720	€10-€69 n=7 467	€70-€239 n=8 232	€240-€999 n=8 503	≥€1000 n=7 467	All n=41 257	p value
Gender ¤								
Male (%)	63.7	64.6	60.5	61.3	66.6	76.5	64.5	**<0.001**
Female (%)	36.3	35.4	39.5	38.7	33.4	23.5	35.5	**<0.001**
Age ¤	53.6 ± 11.4	54.1 ± 10.2	52.8 ± 10.5	52.2 ± 10.4	53.8 ± 9.6	56 ± 8.4	53.5 ± 10.2	**<0.001**
Number of acts ¤	4 623.1 ± 2 524.6	5 184 ± 2 578.9	5 250.2 ± 2 485	5 436.7 ± 2 456.8	5 687.8 ± 2 327.1	6 140.1 ± 2 577	5 358.6 ± 2 509.8	**<0.001**
Size of the commune of exercise ¤								
<2000 inhabitants	28.3	29	32	35	32	27.6	31.2	**<0.001**
>2000 inhabitants	71.7	71	68	65	68	72.4	68.8	**<0.001**
Patients								
Number ¤	1 006 ± 611	1 135 ± 596	1 150 ± 575	1 214 ± 541	1 260 ± 540	1 293 ± 586	1 176.4 ± 577	**<0.001**
0 to 16-year-old (%) ¤	20 ± 8.4	20.3 ± 7.7	20.9 ± 7.5	21.1 ± 7	20.4 ± 6.6	20.2 ± 6.8	20.5 ± 7.3	**<0.001**
16 to 59-year-old (%) ¤	53.5 ± 8.7	53.4 ± 8.1	53 ± 7.6	52.7 ± 7.1	52.9 ± 7	53.7 ± 7.2	53.1 ± 7.6	**<0.001**
60 to 69-year-old (%) ¤	12.4 ± 5	12.2 ± 4.4	12.1 ± 4.3	12.1 ± 4	12.2 ± 3.7	12.1 ± 3.6	12.2 ± 4.2	**<0.001**
≥70-year-old (%) ¤	14.1 ± 8.2	14.1 ± 7.5	13.9 ± 7.2	14 ± 6.8	14.6 ± 6.9	14.3 ± 7.1	14.2 ± 7.2	**<0.001**
Medical fee exemption due to low income (%) ¤	9.7 ± 10.5	9.6 ± 10.2	9.1 ± 9.3	9.1 ± 9	9.1 ± 8.7	10.8 ± 10.1	9.4 ± 9.6	**<0.001**
Long-term illness (%) ¤	28.8 ± 11.2	28.8 ± 10.7	28.2 ± 10.2	28.4 ± 9.7	28.8 ± 9.6	30.4 ± 10.1	28.7 ± 10.3	**<0.001**

Values are shown as percentage for qualitative variables and as mean ± standard deviation for quantitative variables

¤ <1% of missing data; ¤¤ 1% to 2.5% of missing data; ¤¤¤ 2.5% to 4% of missing data.

Appendix 2

Comparison of explanatory variables with the group “None” in multivariate analysis

OUTCOME	Before 2016	€10-69	€70-239	€240-999	>€1 000
Amount reimbursed for drug prescriptions/act (€)	1.20 (-0.11 to 2.50) 0.003	2.11 (0.76 to 3.46) **<0.001**	2.73 (1.40 to 4.06) **<0.001**	3.88 (2.55 to 5.20) **<0.001**	5.33 (3.66 to 6.99) **<0.001**
Antibiotics 16-65 yo* (%)	-1.10 (-1.21 to 0.45) 0.004	-0.26 (-1.21 to 0.49) 0.502	-0.01 (-0.96 to 0.72) 0.973	0.11 (-1.53 to 0.13) 0.779	1.18 (-2.71 to -0.62) 0.015
Benzodiazepines >65 yo (%)	-0.30 (-2.36 to 0.15) 0.005	-0.28 (-1.56 to 1.03) 0.009	-0.15 (-1.29 to 1.26) 0.148	-0.09 (-1.16 to 1.38) 0.423	0.05 (-0.41 to 2.78) 0.691
Benzodiazepines >12 weeks (%)	0.12 (-0.64 to 0.05) 0.377	0.36 (-0.64 to 0.07) 0.010	0.41 (-0.50 to 0.20) 0.003	0.68 (-0.43 to 0.26) **<0.001**	0.58 (-0.38 to 0.49) **<0.001**
ACE inhibitors/ACE inhibitors + sartans (%)	-0.38 (-0.33 to 0.56) 0.132	-0.36 (-0.10 to 0.82) 0.165	-0.12 (-0.04 to 0.86) 0.630	-0.70 (0.23 to 1.13) 0.006	-1.67 (0.02 to 1.14) **<0.001**
Vasodilators >65 yo (%)	0.01 (-0.09 to 0.11) 0.708	0.05 (-0.05 to 0.16) 0.087	0.09 (-0.01 to 0.19) 0.003	0.10 (0.00 to 0.20) **<0.001**	0.15 (0.03 to 0.28) **<0.001**
Generic antibiotics (%)	-0.66 (-1.22 to -0.10) **<0.001**	-0.87 (-1.45 to -0.30) **<0.001**	-1.24 (-1.81 to -0.67) **<0.001**	-1.83 (-2.40 to -1.27) **<0.001**	-2.17 (-2.88 to -1.47) **<0.001**
Generic antihypertensive drugs (%)	-0.60 (-1.01 to -0.18) **<0.001**	-1.01 (-1.43 to -0.58) **<0.001**	-1.51 (-1.93 to -1.08) **<0.001**	-2.61 (-3.03 to -2.19) **<0.001**	-4.24 (-4.77 to -3.72) **<0.001**
Generic statins (%)	-2.76 (-3.65 to -1.88) **<0.001**	-4.35 (-5.27 to -3.44) **<0.001**	-5.83 (-6.73 to -4.94) **<0.001**	-8.36 (-9.25 to -7.46) **<0.001**	-12.14 (-13.26 to -11.03) **<0.001**

Values are the adjusted mean differences, with their 99.9% confidence interval and the corresponding p value

Appendix 3

Results of the adjusted analyses in which the different GP groups were replaced by the median amount of benefits for each group. The groups “None” and “Before 2016” were grouped together as having received no benefit in 2016.

Outcome	Beta coefficient	Standard error	P value
Amount reimbursed for drug prescriptions/act (€)	0.00280	0.00026082	**<.0001**
Antibiotics 16-65 yo* (%)	0.00148	0.00020137	**<.0001**
Benzodiazepines >12 weeks (%)	0.00032194	0.00008757	**0.0002**
Vasodilators >65 yo (%)	0.00008536	0.00001969	**<.0001**
Benzodiazepines >65 yo (%)	0.0001819	0.00006808	0.0075
ACE inhibitor/ACE inhibitors + sartans (%)	-0.00092337	0.00016228	**<.0001**
Anti-platelet aggregation drugs (%)	-0.00022872	0.00010071	0.0231
Generic antibiotics (%)	-0.00113	0.00011024	**<.0001**
Generic PPIs (%)	0.00001348	0.00000872	0.1219
Generic antidepressants (%)	-0.00013475	0.00009769	0.1678
Generic statins (%)	-0.00640	0.00017385	**<.0001**
Generic antihypertensive drugs (%)	-0.00247	0.00008188	**<.0001**

Values are the adjusted mean difference, their corresponding standard error and p value

Association between benefits paid by pharmaceutical companies to French general practitioners and their drug prescriptions in 2016: a retrospective study using the French Transparency in Healthcare and National Health Data System databases

Bruno Goupil[1], Frédéric Balusson[2], Florian Naudet[3,4], Maxime Esvan[3], Benjamin Bastian[1,3], Anthony Chapron[1,3], Pierre Frouard[1]

[1]Department of General Medicine, University Rennes 1, Rennes, France; [2]EA 7449 (Pharmacoepidemiology and Health Services Research) REPERES, Univ Rennes, Rennes University Hospital, Rennes, France; [3]Univ Rennes, CHU Rennes, Inserm, CIC 1414 [(Centre d'Investigation Clinique de Rennes)], F- 35000 Rennes, France; [4]Department of Adult Psychiatry, Rennes University Hospital, Rennes, France

Correspondence to: P Frouard pierre.frouard@gmail.com

Abstract

Objectives

To evaluate the association between benefits (donated equipment, meals, transport, accommodation, etc.) paid by pharmaceutical companies to French general practitioners (GP) and their prescribing behaviours for some drugs.

Design

Retrospective study of data from the French Transparency in Healthcare and National Health Insurance databases.

Setting

Primary care, France.

Participants

41 257 GPs, who throughout 2016 worked exclusively in the private sector and had at least five patients, were divided in six groups in function of the monetary value of the received benefits reported by pharmaceutical/medical device/other health-related companies in the Transparency in Healthcare Database.

Main outcome measures

The main outcome measures were 11 prescription efficiency indicators used to calculate the GPs' performance-related financial incentives by the French National Health Insurance, and the amount reimbursed by the National Health Insurance for drug prescriptions per act. Physicians and patients' characteristics were used as adjustment variables. The significance threshold of 0.001 was used for all statistical analyses.

Results

The amount reimbursed by the National Health Insurance for drug prescriptions per act was lower in the GP group with no benefit reported in the Transparency in Healthcare Database in 2016 and since its launch in 2013 ("None" group) compared with the GP groups with at least one benefit in 2016 ($p<0.001$). The "None" group also prescribed more generic drugs for antibiotics, antihypertensive drugs and statins compared with physicians with at least one benefit between 2013 and 2016 ($p<0.001$). The "None" group also prescribed fewer benzodiazepines for more than 12 weeks and vasodilators compared with physicians with ≥€240 reported benefits in 2016, and fewer angiotensin converting enzyme (ACE) inhibitors in relation to all ACE and sartan prescriptions compared with physicians with ≥€1000 reported benefits in 2016 ($p<0.001$). Differences were not significant for the prescription of aspirin and generic drugs for antidepressants and proton pomp inhibitors.

Conclusion

French GPs who do not receive any benefit from pharmaceutical companies have better prescription efficiency indicators and less costly drug prescriptions than physicians receiving benefits. As this is an observational study, it is susceptible to residual confounding and no causal relationship can be drawn. Nevertheless, our results reinforce the hypothesis that pharmaceutical companies influence the GPs' prescribing behaviour, and give some insights into the extent of their interference.

Trial registration

OSF registration number: OSF.IO/8M3QR

What is already known on this topic

Drug promotion is linked to less rational and more costly drug prescriptions

French general practitioners are exposed to benefits from pharmaceutical companies (donated equipment, meals, transport, accommodation, etc.).

What this study adds

Our study suggests that French general practitioners receiving no benefit from pharmaceutical companies have better prescription efficiency indicators (as defined by the National Healthcare Insurance) and less costly drug prescriptions than those receiving benefits.

Introduction

Healthcare professionals are highly exposed to pharmaceutical marketing/promotion activities. Many evidences suggest that physicians' exposure to pharmaceutical promotion has a negative impact on the quality and quantity of drug prescriptions, resulting in lower quality of care, exposure of patients to unjustified risks and/or more costly prescriptions.[1,2] To address this issue, some countries have implemented legislations, such as the US Physician Payments Sunshine Act, to appreciate the extent of the links between pharmaceutical companies and physicians.[3] The relevance of these policies on the prescription behaviour is controversial.[4,5] In France, following the health scandal concerning benfluorex (Mediator®), the French version of the "Sunshine Act" legislation was put in place in 2011, including the creation of the Transparency in Healthcare Database.[6] This database collects and makes accessible all data declared by pharmaceutical/medical device/other health-related companies on their links with healthcare professionals/organizations, on Internet since 2013. Companies must fill in a declaration that is publicly accessible through a dedicated website hosted by the French Health Agency. Benefits (i.e., any type of gift or payment given by a company to a healthcare actor without any counterpart) are among the links of interests reported in this database. They include donations of equipment, invitations, catering expenses, handling of leisure travel, and cash payments such as commissions, rebates or reimbursement of expenses. Benefits must be declared (amount, nature, identity of the receiver, and date) starting from €10 including taxes.

Drug prescriptions by French physicians can be analysed using the National Health Data System ("Système National des Données de Santé") that merges information on the reimbursement claims coming from

all French healthcare insurances.[7] It covers nearly the whole French population. It includes anonymous data on patients, data on prescribers, physician visits, prescriptions, chronic medical conditions, etc. It is used for multiple purposes, including calculating the prescription efficiency indicators for the performance-related financial incentives of physicians ("Rémunération sur Objectif de Santé Publique").[8]

These two databases (Transparency in Healthcare Database and National Health Data System) offer the unique opportunity to investigate the issue of the influence of benefits on the French general practitioners (GPs)' prescribing behaviour. Therefore, in this study, we evaluated the association between benefits reported in the Transparency in Healthcare Database and drug prescriptions made by French GPs in 2016. As pharmaceutical promotion is expected to influence the prescription quality, quantity and cost, we hypothesized the existence of an association between receiving benefits and poorer quality and more costly prescribing patterns.

Methods

Data sources

This retrospective study was conducted by matching the benefits reported in the Transparency in Healthcare Database with data from the National Health Data System. After loading the Transparency in Healthcare Database from www.data.gouv.fr, we calculated the total monetary value of the benefits listed for each GP in 2016. We included also GPs without any benefit listed for 2016. For each GP, we also calculated the total monetary value of the benefits received in 2013 and 2015, to differentiate between GPs who did not and GPs who did receive benefits in the last 4 years (up to 2016). Under an agreement with the National Health Insurance, we could extract from the National Health Data System the prescription efficiency indicators used for the performance-related financial incentives, the amount reimbursed for drug prescriptions per act in 2016, and the GPs and patients' sociodemographic data.

We focused on 2016 data because of the long administrative procedure to obtain the authorization to access the National Health Data System. Indeed, we submitted our first application on 31 August 2017. We registered a protocol detailing the analysis plan on 17 January 2018 (OSF registration number: OSF.IO/8M3QR, in French). We obtained the ethical approval by the Commission Nationale Informatique et Liberté on 24 May 2018 (CNIL registration number: DR-2018-089). Data were available on a secured remote portal on 21 November 2018.

Study population

We included all GPs who worked in metropolitan France and the overseas territories for the entire 2016 year (from 1 January 2016 to 31 December 2016). To obtain a study population as homogeneous as possible, we excluded: i) GPs who worked with a particular mode of exercise (allergists, angiologists, geriatricians, emergency physicians, and other modes listed by the National Health Insurance); ii) GPs who did not work exclusively in the private sector, as normally done in France (i.e., GPs employed by a public healthcare institution, or who had a double activity, in the private sector and in a public healthcare institution); iii) GPs who did not work the entire year 2016; and iv) GPs who reported less than five patients. These exclusion criteria were based on National Health Data System information.

Study groups

We divided the study population in six groups according to the amount (or the lack) of benefits reported in the Transparency in Healthcare Database. This was necessary to compare GPs while preserving their anonymity. The first group included GPs without reported benefits in 2016 and since the launch of the Transparency in Healthcare Database in 2013 (group "None"). The second group included physicians without reported benefits in 2016, but at least one benefit between 2013 and 2015 (group "Before 2016"). The third group included physicians with significant benefits in 2016, arbitrarily defined as a cumulative benefit amount higher than or equal to €1000 including taxes (group "≥€1000"). We divided the remaining GPs in three groups of equivalent size to study the influence of small benefits (group "€10-€69"; group "€70-€239"; group €"240-€999"). We took into account all benefits reported for the year 2016, but for those smaller than €10 including taxes because they are not reported in the Transparency in Healthcare Database.

Database linkage

We recruited GPs from the comprehensive list of GPs by the National Council of the College of Physicians ("Conseil National de l'Ordre des Médecins") received on 17 August, 2017. First, we matched the GPs with the data from the Transparency in Healthcare Database downloaded on 5 April 2018, using their unique National Healthcare Professional Registry ("Répertoire Partagé des Professionnel de Santé") identification number. Then, the National Health Insurance database matched the GPs with the National Health Data System using their family name, first name, and postal code of the commune of exercise available in our list and in the National Health Data System (no identification number was available in the National Health Data System). Finally, 6.2% of all listed GPs could not be included because the second matching could not be performed.

Explanatory variables and outcomes of interest

Every year, the National Health Insurance calculates various indicators for the GPs' performance-related financial incentives. In 2016, 11 prescription efficiency indicators were used with the aim of promoting or limiting the prescription of some drug classes in function of their benefit-risk balance, or of limiting the cost of prescriptions by promoting generic drugs. The 11 indicators were: percentage of patients treated with low-dose aspirin among patients treated with anti-platelet aggregation drugs; percentage of patients treated with antibiotics among all 16 to 65-year-old patients; percentage of >65-year-old patients treated with long half-life benzodiazepines; percentage of patients treated with benzodiazepines for more than 12 weeks among patients treated with benzodiazepines; percentage of angiotensin converting enzyme (ACE) inhibitor prescriptions relative to all ACE inhibitor and sartan prescriptions; percentage of >65-year-old patients treated with vasodilators; percentage of generic drug prescriptions for antibiotics; percentage of generic drug prescriptions for antidepressants; percentage of generic drug prescriptions for antihypertensive drugs; percentage of generic drug prescriptions for proton pump inhibitors (PPIs); and percentage of generic drug prescriptions for statins.

We considered these 11 prescription efficiency indicators (11 variables), and the amount reimbursed by the National Health Insurance for drug prescriptions per act in 2016 (1 variable) as outcomes of interest.

Covariates

We used the following covariates available in the National Health Data System that could influence drug prescriptions as variables for adjustment: GPs' characteristics (age, sex, size of the commune of exercise [more or less than 2000 inhabitants], number of acts performed per year), and patients' characteristics (number of patients reported as attending, age distribution, proportion of patients with medical fee exemption status due to low-income or long-term conditions).[9]

Patient and public involvement

We did not include patients as study participants. Patients were not involved in the research question or the study design. We do not plan to involve patients in the dissemination of results, and we will not disseminate results directly to patients.

Statistical analyses

To describe the study population, we assessed differences among GP groups using the Chi2 test for qualitative variables and ANOVA for quantitative variables. Then, we used a two-step strategy to answer our research question. First (primary analyses), we identified significant differences among at least two GP groups for each of the 12 variables to be explained. Then (secondary analyses), for variables with significant differences between groups in the primary analyses, we compared each group to the group that was less exposed to benefits (i.e., the group "None").

Primary analyses

We did the primary analyses using a linear model. After univariate analysis, we performed a multivariate analysis with the different Transparency in Healthcare GP groups and the potential confounding factors (i.e., covariates: GPs and patients' characteristics) identified as associated with the outcome (threshold: p=0.25). We used a step-by-step strategy to retain the most parsimonious model and verified the application conditions of the final model. We chose a significance threshold of 0.001 for all statistical analyses. This is slightly more conservative that the Bonferroni's correction with a threshold of 0.05 that takes into account the 12 different outcomes analysed.

Secondary analyses

On the basis of literature data, we hypothesized that the group "None" should have the best prescribing behaviours, and used this group as reference group to explore the differences detected in the primary analyses (significance threshold of 0.001).

Additional analyses

We performed two additional exploratory analyses that were not planned in the initial protocol. First, to determine whether the associations observed across GP groups could be explained by the amount of the reported benefits, we performed multivariate analyses by replacing the different groups by the median monetary value of benefits for each group (the groups "None" and "Before 2016" were grouped together as having received no benefit

in 2016). We then performed the post-hoc sensitivity analyses after excluding the first and last percentiles of each explanatory variable and covariate to test the effect of extreme values on the results.

For all statistical analyses, we used the SAS software 9.4 (SAS institute, Cary N.C, USA). As we were not allowed to export the National Health Data System data, we analysed them in the National Health Data System remote portal.

Changes in the initial protocol

We updated the Transparency in Healthcare data on April 5, 2018. This slightly changed the size of the different GP groups. We excluded from the analysis GPs who reported less than five patients because they were not eligible for any performance-related incentive. In multivariate analyses, we had to split patients in two age groups (younger and older than 60 years of age). This choice was based on the fact that the ≥60-year-old population seemed to be the most important group for prescriptions.[9]

Results

Selection of the study population

We included 41 257 GPs for analysis among the 53 763 French GPs identified in the National Council of the College of Physicians list. For 3 338 GPs, their name and postal code in the National Council of the College of Physicians could not be matched in the National Health Data System lists These physicians belonged more often to the group "None" (16%) than the other groups (2.5% to 5.3% according to the group). We excluded 9 168 GPs based on the exclusion criteria (fig 1).

[insert here Figure 1]

Figure 1 Study flowchart.

Description of the study population

The included GPs had a mean age of 53.5 ± 10.2 years and 64.5% were men. They performed 5 359 ± 2 510 acts for 1 681 ± 774 patients, and 12 857 (31.2%) exercised in rural areas. Among the 41 257 GPs included in the study, 36 232 (87.8%) were listed in the Transparency in Healthcare Database as having received some benefits. Comparison of the GPs and patients' characteristics (i.e., variables used for adjustment) using the ANOVA and Chi2 tests highlighted significant differences among the GP groups ($p<0.001$) for all covariates (Appendix 1). Particularly, GPs in the group "None" had the lowest mean activity (4 623 ± 2 525 acts) and the smallest mean number of patients (1 006 ± 611 patients), while physicians of the group "≥€1000" had the highest activity (6 140 ± 2 577 acts) and the largest number of patients (1 293 ± 585 patients). Physicians in the group

"≥€1000" were mostly men (76.5%), and they had the highest percentage of patients with long-term conditions (30.4% ± 10%). Between 0% and 0.70% of data were missing for these variables.

Primary analyses

Univariate and multivariate analyses (table 1) highlighted significant differences among GP groups ($p<0.001$) for the following outcomes: amount reimbursed for drug prescriptions per act, proportion of antibiotic treatments for 16 to 65-year-old patients, percentage of >65-year-old patients treated with long half-life benzodiazepines, percentage of patients treated with benzodiazepines for more than 12 weeks compared with all patients treated with benzodiazepines, percentage of ACE inhibitor prescriptions relative to all ACE inhibitor and sartan prescriptions, percentage of >65-year-old patients treated with vasodilators, percentage of generic drug prescriptions for antibiotics, antihypertensive drugs and statins. Missing data for the 12 outcome of interest ranged from 0.60% to 3.06%.

[insert here Table 1]

Table 1 Primary analyses

Values are the mean ± standard deviation

¤ <1% of missing data; ¤¤ 1% to 2.5% of missing data; ¤¤¤ 2.5% to 4% of missing data

Secondary analyses

Analysis of the differences between the group "None" and the other GP groups for the 12 variables identified in the primary analyses are presented in fig 2 and Appendix 2. This analysis highlighted that compared with the "None" group, the amount reimbursed for prescribed drugs/act significantly increased, and the percentage of generic drug prescriptions for antibiotics, antihypertensive drugs and statins significantly decreased for most groups.

[insert here Figure 2]

Figure 2 Comparison of explanatory variables with the group "None" in multivariate analysis

Values are the adjusted mean differences and their corresponding 99.9% confidence interval

Additional analyses

Except for the proportion of >65-year-old patients treated with long half-life benzodiazepines (p=0.0075), the associations observed in the primary analyses were also found using the median monetary value of benefits for each group (instead of the group as a class), suggesting a dose-dependent association between benefits and eight indicators (Appendix 3).

Finally, sensitivity analyses performed after excluding the first and last percentiles of each explanatory variable and covariate gave similar results (data not shown).

Discussion

Principal findings

In this retrospective study, we found an association between benefits paid by pharmaceutical companies to French GPs and nine of the twelve indicators studied for the year 2016.

The amount reimbursed for prescribed drugs per act was significantly lower for the group "None" compared with the groups €10-€69, €70-€239, €240-€999 and ≥€1000. GPs in the Group "None" prescribed significantly more generic drugs for antibiotics, antihypertensive agents and statins compared with all other groups, including the group "Before 2016". They also prescribed significantly fewer benzodiazepines for more than 12 weeks and vasodilators compared with the groups "€240-€999" and "≥€1000", and significantly fewer ACE inhibitors compared with the group "≥€1000". Conversely, we did not find any association for the percentage of patients treated with low-dose aspirin among patients treated with anti-platelet aggregation drugs, and for the prescription of generic drugs for antidepressants and PPIs. The high proportion of generic drug prescription for PPIs (around 99.9% in all groups) and antidepressants (around 91% in all groups) and the absence of differences between groups may be explained because in 2016, PPIs did not have a patented originator molecule, and the few patented antidepressant drugs on the market were "old" drugs not concerned by active promotion from pharmaceutical companies.[10] Finally, compared with the group "None", we did not find any difference in the percentage of antibiotic treatments for 16 to 65-year-old patients and of long half-life benzodiazepines for >65-year-old patients.

Strengths and limitations of the study

This study has several strengths. To our knowledge, this is the first analysis matching data from the French Transparency in Healthcare Database with data from the National Healthcare Data System for comparative

analysis of the GPs' prescribing behaviours. We tried to reduce confounding bias by taking into account the main available confounders in the multivariate analysis.[9] The use of databases is an effective way to explain and highlight prescribing behaviour differences that are minimized in declarative studies on the influence of pharmaceutical promotional actions.[2] The external validity of our results is underlined by the concordance of the mean values of the indicators calculated for our population with the national averages.[8]

Our study has some limitations. We do not know whether all benefits are fully mentioned or the extent of misinformation in the Transparency in Healthcare Database because it is only based on the statement made by pharmaceutical companies without effective control.[5] The 6.2% of failed matches for GPs might have introduced bias, especially because the matching failure rate was different among the GP groups.

Confounding is a major issue in observational research and there is no perfect way to handle it. Methods, such as computation of E-values, have been proposed, but they have many caveats.[11] Despite the adjustment of the analysis to various available factors that might influence the prescribing behaviour, we could not take all of them into account. For instance, we did not include other means of pharmaceutical promotions, type of GP activity (in group or alone), status of university internship supervisor, etc. Therefore, the study is prone to residual confounding. Receiving benefits from pharmaceutical companies and receiving performance-related incentives from the National Health Insurance may be influenced by the same factors. In addition, in the absence of clinical data, we could not have a full picture of the reasoning leading to each prescription.[12]

Our literature search did not find a unique and/or validated indicator to evaluate in a general way the GPs' prescription quality.[13] Therefore, we used multiple indicators validated by the French National Health Insurance to assess prescribing behaviours. Some of them are also used in drug utilization studies.[14] However, their validity is somehow questionable.[15]

Performance-related financial incentive indicators were not available for 0.64% to 3.04% of GPs, which roughly corresponds to the 2.8% of refusals from physicians to collaborate in this process.[16] Such missing data may be associated with both the benefits perceived and the GP's prescription pattern.

Finally, it is not possible to conclude that the different prescription patterns are caused by pharmaceutical promotion activities. An alternative explanation could be that GPs receiving benefits may be more targeted and/or receptive to pharmaceutical marketing because they have specific prescribing behavious.[2] All these possible caveats suggest that these findings should be interpreted with caution, and they preclude any definitive conclusion in terms of causality.

Results consistent with the literature

These results are consistent with recent meta-analyses and systematic reviews showing an association between pharmaceutical company gifts and more frequent, lower-quality and more costly prescriptions.[17–20] Two recent studies also found a lower prescription rate of generic drugs by physicians who benefit from pharmaceutical companies. [21,22] According to Health Action International, no study has demonstrated health benefits from pharmaceutical promotion activities.[1,2]

Our post-hoc analyses suggest a possible gradual association between benefits paid by pharmaceutical companies and the cost of drug prescriptions per act and prescription efficiency indicators. A similar observation was reported by two large retrospective studies in the United States in 2016.[23,24]

Our study show a significant difference between the group "None" and the group "Before 2016" for generic drug prescription of antibiotics, antihypertensive agents and statins, suggesting that the observed association could be also observed over time.

Health and economic impacts

The more frequent use of some drugs, such as benzodiazepines and vasodilators, increases the risk of well-known adverse effects of these molecules, with sometimes serious or even fatal consequences. Our data suggests that their prescription slowly but progressively increases from the "None" to the "≥€1000" group. Prescriptions of brand name drugs instead of generic drugs represent an additional cost for the National Health Insurance with no proven benefit for the patient. In France, the price of a generic drug is at least 60% lower than the price of the original drug.[25] With an additional €1.2 to €5.3 reimbursed per prescription, GPs with benefits reported in the Transparency in Healthcare database are associated with an important additional charge for the National Health Insurance compared with physicians who did not have any benefit reported. Notably, among the twelve indicators we used, the most significant were directly linked with economic issues: cost of drug prescription per act, and generic drug prescription. This is in line with studies showing that pharmaceutical promotion targets market issues in priority.[1,2]

In our study, associations were also significant for the "€10-€69" group. Differences in prescribing behaviours after small gifts have been reported by several studies and are based on donation and counter-donation mechanisms that have been well described by humanities and social science studies.[26–28] Benefits are gifts that lead to a sense of accountability and ultimately negatively influence the prescribing habits.[29] More generally, the amount of benefits reported represents for most physicians only a little or very little part of their annual income, and for pharmaceutical industries a small financial engagement compared with their benefits in terms of drug selling.[2]

Results in favour of the influence of benefits on prescriptions

Before the creation of the Transparency in Healthcare Database, the scope and frequency of benefits paid by pharmaceutical companies to French GPs were not easily accessible. Our study shows that benefits to GPs are common and associated with less rational prescriptions for patients and more expenses for the National Health Insurance. Although the causal links must not be made, the results of our study are in line with the existing literature, and reinforce the hypothesis that pharmaceutical companies influence GPs' prescribing behaviours. Future research should assess the association between prescribing behaviour and conventions, another link of interests reported in the Transparency in Healthcare Database involving obligations on both sides (such as speaker in a conference), and evaluate these features also in specialist doctors and particularly among the so-called Key Opinion Leaders.[2]

Perhaps, the time has come for interventional studies to test prospectively the impact of restrictive policies on physicians' prescription patterns.

We thank Medhi Gabbas for extracting data from the National Health Insurance database. We thank Elisabetta Andermarcher for English editing. We thank Emmanuel Allory, Irène Frachon, Emmanuel Oger, Dominique Somme, and Bruno Toussaint for their help.

Contributors: BG and PF jointly initiated, designed the study, searched the literature, interpreted the results and wrote the manuscript. FB performed the analysis and interpreted results. FN and ME jointly contributed to the study design and interpreted results. BB contributed to the study design. AC contributed to the study design and offered institutional support. All authors have critically revised the manuscript for important intellectual content and approved the manuscript. The corresponding author attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted. PF is guarantor.

Funding: University Hospital Rennes 1, Rennes, France, paid for the English editing and the publication fees. It had no role in the design, the collection, the analysis, the interpretation of data, the writing of the report and the decision to submit for publication. BG, PF and AC are independent from funder. FB, FN, ME, BB are partially employed by funder. All authors had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Competing interest: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: research support for the submitted work as described above; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; AC reports personal fees and non-financial support from Roche, personal fees and non-financial support from Novartis Pharma, personal fees from Congrès colloques conventions, outside the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The French Commission Nationale Informatique et Libertés approved this study: authorization CNIL DR 2018-089 on 24/05/2018. A letter has been delivered to all French URPS ("Unions Régionales des Professionnels de Santé") to inform general practitioners of the objective of the research and give them the right to oppose.

Data sharing: Data from Transparency in Healthcare Database are available on www.data.gouv.fr. We cannot share National Health Data System data as they are only available on a secure portal. Authorization to access this portal needs registration and clearance.

Transparency: The guarantor affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspect of the study was omitted; and that any discrepancies from the study as originally planned have been explained.

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