High and daily exposure to precariousness negatively impacts the prescriptions of general practitioners to precarious populations: an observational pharmaco-epidemiological study investigating inequalities in access to health care in France

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Abstract

Background

The association between precariousness and lack of access to health care is well-documented. Prescribing drugs is one promising marker for this health care inequality. A recent study, carried out on the entire French population, has developed a new measurement model based on the 20 most prescribed molecules. It reports that drugs, targeting diseases known to more affect precarious populations, are under-prescribed by general practitioners (GP) to these populations. If these findings highlight unequal drugs prescriptions between populations despite epidemiological factors, it is still unknown whether a high and daily exposure to precariousness negatively impacts GPs prescriptions. Here, we investigated whether there are more inequalities in prescriptions of GPs who are highly and daily exposed to precariousness, compared to GPs who are less exposed to precariousness.

Methods

This retrospective pharmaco-epidemiological study compared the Defined Daily Dose relative to different reimbursed drugs prescribed by GPs to precarious and non-precarious patients in four French regions respectively with low and high precariousness prevalence in 2015. Data were analyzed using repeated-measures ANOVAs (Sphericity correction: Greenhouse-Geisser; *Post-Hoc* Tests, Bonferroni corrected).

Results

2 out of 20 molecules were significantly over-prescribed (tamsulosine and timolol) and 7 were under-prescribed (amoxicillin, econazole, ciclopirox, prednisolone, paracetamol, cromolyn sodium, ibuprofen) to precarious populations in regions with high precariousness prevalence.

Conclusions

The over-reimbursement of tamsulosine and timolol did not reflect the negative impact of exposure to precariousness on the GPs prescriptions but a failure of the health system to compensate for inequalities in access to chirurgical treatments. In contrast, the under-reimbursement of amoxicillin, ciclopirox and econazole indicated an effect of the exposure to precariousness on GPs' prescriptions, these molecules targeting acute diseases that affect more significantly precarious than non-precarious populations. The same explanation is probably suitable for the under-reimbursement of prednisolone, paracetamol, cromolyn sodium, and ibuprofen, although their various indications render difficult to delimitate the clinical purpose at the basis of their prescription. We assume that exhausting working conditions, repeated exposures to difficult living conditions, and repeated experiences of failure impairs empathic skills in GPs, leading to burnout which negatively impacts the quality of care and, thus, prescriptions.

Background

The association between poorer health (e.g., higher incidence of mental disorders, cancers, vascular diseases) and lower income is well-documented [1]. As featured by Moscrop and McPherson [2], income data are seldom collected in routine primary care. And this, although precarious people see their general practitioners (GP) more frequently than the general population, and primary care is the point of first contact between health systems and precarious people [2]. Therefore, determining the interactions between lower income and health inequalities is essential for care efficiency.

In France, policies to control drug expenditure rely upon economic models aiming to improve efficacy and reduce inappropriate prescriptions, overconsumption and iatrogenesis [3, 4]. These policies generate savings in the short term. These are also supposed to decrease inequalities in access to health care, permitting precarious people to benefit from free health expenditure. The French Health System is complex (for more details, see Birault et al. [5]). Basically, people with a monthly income below EUR 720 for a single person and EUR 1080 for a couple living in urban areas are considered “precarious”. In France, 89% of the population benefits from health care cover. The French Health System reimburses both precarious and non-precarious people up to 65% of their health expenditure. Concerning the remaining 35%, non-precarious populations can sign up to additional private insurance, enabling them to be fully reimbursed (100%). In contrast, people in precarious situations benefit from support of the French Healthcare System and are automatically reimbursed up to 100%. This “Universal Medical Coverage” (CMU), introduced in 2000, has been importantly amended and its functioning significantly improved in 2015. 5,4 millions of individuals have been concerned by this measure (8.21%).

Precarious populations (i.e., CMU-beneficiaries) present with specific medical characteristics. For example, in these populations, there is a risk factor of 1.4 for end-stage chronic kidney disease, cardiovascular or neurological disease, 2 for epilepsy, 2.2 for diabetes, 2.4 for psychiatric illnesses, 4.7 for addictive disorders [6]. The same is also observed for obesity (15.4% against 9.0% in the general population) [6]. Moreover, health expenditure is higher in precarious populations. Two main factors can explain this fact. Firstly, precarious people see their GP more frequently, generating a significant increase of drug costs [7, 8]. Secondly, higher incidence of chronic diseases in these populations induces higher mortality [8]. Normally, if these two factors and the financial compensation for equal care access are controlled for, precarious populations should receive the same prescriptions as non-precarious populations. This is not the case. Indeed, in a previous pharmaco-epidemiological study, we have recently shown that six molecules (metformin, atorvastatin, rosuvastatin, tamsulosine, paracetamol, and timolol) are significantly less reimbursed and, thus, less prescribed, in precarious populations [5]. These differences were not explained by a specific epidemiology.

Hence, if the financial compensation does not reach the target, attention should be paid to the functioning of the health care system. As mentioned above, primary care is often the point of first contact between health services and precarious populations [2]. Moreover, French GPs have obligations to care for precarious people following a contract they signed with the French Healthcare System. But if GPs

intend to promote equal access to care, why is this equality not reached in fact? In others words, examining the link between prescribers, prescriptions, patients' populations and physicians-patients interaction is needed to better understand and improve the equal access to health care and the efficiency of health cover in precarious populations.

We assume that the characteristics of precarious populations and how these impact GPs prescriptions are an interesting candidate to explain the unequal access to care observed. However, two opposite hypotheses can be considered. Firstly, it is plausible that a well-trained GP, working for a long time with precarious populations, has developed specific knowledge and skills to better care for these populations, leading to a greater efficiency. Conversely, it can be also posited that the daily confrontation with precarious populations, known to be more difficult to care for [9], leads to an alteration of empathy, which is one indispensable skill in caregiver [10, 11] and, thus, burnout syndrome [10, 12]. The consequences of which are deleterious for the quality of care. In the end, the question of the interaction between quality of care – reflected in appropriate prescriptions – and GPs exposure to precarious populations is much more complex than originally thought. Therefore, further exploring this interaction is necessary to compensate for possible failures in the health system. Moreover, in the context of the current pandemic, better determining the link between inequalities in access to health care and precariousness has become an urgent issue. Indeed, extreme poverty has been predicted to significantly increase and to be multiplied by a factor of 5 due to Covid-19 [13].

We here address the following question: is there a link between the exposure of prescribers to precariousness and the increase of inequality of prescriptions? For that, we applied the same pharmaco-epidemiological approach as in our previous study, carried out on the entire French national population [5], to four regional populations. The rational was that these four regions present with large differences of precariousness prevalence. We compared four regions with respectively a low (Brittany Region and Center Region) and high (Overseas Region and Occitany Region) precariousness prevalence. We hypothesized that there are more inequalities in prescriptions of GPs who are highly and daily exposed to precariousness than GPs who are less exposed to precariousness.

Methods

We used the same methods as in our previous study [5].

Study Period

Similarly to our previous study, the present study focused on the year 2015 (see below "Data collection and analysis").

Data Collection and Analysis

Data were obtained and collected from the French Statistic Institute for Private Practitioners ("Institut Statistique des Professionnels Libéraux" or ISPL). ISPL enables the aggregation of data, regarding drugs

reimbursement, from the French Health Insurance System and insurance providers. Permission to contact ISPL and to collect data from its database is only rarely obtained. Accordingly, we were not allowed to collect data relative to the patients' age, gender, underlying medical conditions, etc. Moreover, we were allowed only to collect data from the year 2015 (which is a key step in the CMU history; see introduction). Thus, only data relative to yearly drugs reimbursement (in 2015) were extracted from the ISPL database.

Data Selection Relative to Prescribers' and Patients' Populations

Analyses were computed on the yearly reimbursement rates of drugs prescribed in 2015 by GPs to both precarious (P) and non-precarious populations (NP). This was done for two main reasons. Firstly, GPs prescribe to the entire French population, regardless of gender. As an example, this is not the case for urologists, gynecologists or midwives. Secondly, we focused on primary care and not on medical care specialties, as precarious populations have been reported to see their GPs more frequently than specialists. Moreover, we focused on four French regions with various prevalence of precariousness on the basis of the CMU annual statistics report. This was done to investigate the impact of the precariousness gradient on the GPs medical prescriptions.

Firstly, we selected two regions with a comparable amount of insured populations, i.e., the Brittany Region (BR) and Center Region (CR). BR and CR have the two lowest amounts of insured populations in France.

- **BR**: 3,341,188 insured people, including 149,115 precarious individuals (4.46% of the regional population). We selected BR as it has the lowest CMU population, compared to other French regions.

- **CR**: 2,635,080 insured people, including 172,758 precarious individuals (6.56% of the regional population).

Secondly, we selected two regions with a different amount of insured populations, similar and high CMU populations, and, consequently, different CMU prevalence, i.e., the Overseas Region (Guadeloupe, Guyana, Martinique and Réunion) (OSR) and Occitany Region (Languedoc Roussillon and Midi Pyrenees) (OCR).

- **OSR**: 1,890,901 insured people, including 613,453 precarious individuals (32.44% of the regional population). OSR has the highest CMU prevalence in France.

- **OCR:** 5,771,360 insured people, including 515,259 precarious individuals (8.82% of the regional population).

Data Selection Relative to Medications and Criterion of Principal Evaluation

For medications, we used the Anatomical Therapeutic Chemical (ATC) classification. The World Health Organization (WHO [14]) Collaborating Centre for Drug Statistics Methodology is in charge of this classification. Medications are divided into different groups according to the organ or system on which they have an action, and according to their therapeutic and chemical features. This classification is based on five levels. Respectively, the 1st level (first letter) indicates the anatomical group (among 14

different ones); the 2nd level (first two numbers) the main pharmacological or therapeutic subgroups; the 3rd and 4th levels (second and third letters) the therapeutic, pharmacological or chemical subgroups; and the 5th level (last two numbers) the chemical substance. This classification allows a therapy to be apprehended via analysis of the pharmaceutical used. As an example, metformin is a chemical substance corresponding to the 5th level (defined by letters and numbers as follows: A10BA02), which belongs to the chemical group of biguanides (4th level, A10BA) representing the pharmacological family of hypoglycemic agents (3rd level, A10B), a component of the therapeutic family of drugs indicated in diabetes (2nd level, A10), belonging to the anatomical group of the digestive system (1st level, A) (Table 1).

We used the Defined Daily Dose (DDD) as a criterion of principal evaluation. That is, we hypothesized that differences in reimbursed drugs prescriptions are reflected in DDD modulations for given molecules between populations (same as in Birault et al. 2020 [5]).

Drugs consumption can be expressed in cost, number of units, number of prescriptions, or by the physical quantity of drugs. DDD is a technical unit of measurement and is determined by WHO. It refers to the assumed average maintenance dose per day for a drug used for its main indications in adults. DDDs are only assigned for medicines given with an ATC code. DDD is notified on each pack by the producer and corresponds, thus, to a daily cost. Applying DDD enables to test for changes in drugs utilization over time, to compare and evaluate the effect of an intervention on drug use, to document the relative therapy intensity with various groups of drugs, to track changes in the use of a class of drugs, and to evaluate regulatory effects and effects of interventions on prescribing patterns [14].

Here, the expenditure rate was collected based on the DDD per patient over 20 years of age for each pharmaceutical form and for each selected molecule in 2015. For each ATC class, we selected two molecules, i.e., depending on two criteria. That is, the molecule with the highest total cost of reimbursement and the molecule with the highest amount of packs reimbursed. We used this methodology as some molecules are sold at a high price, i.e., in packs containing only low daily doses (i.e., for short-lasting treatments) (e.g., amoxicillin). In contrast, some molecules are sold at lower prices, i.e., in packs containing more daily doses (i.e., for long-lasting treatments) (e.g., atorvastatin). When a given molecule for a given ATC class responded equally to these two criteria (total cost of reimbursement and total amount of packs reimbursed), this was uniquely retained. For given ATC classes, there was, thus, only one molecule selected. We here note that the antineoplastic class L was excluded, as GPs are not the prime prescribers for this class.

Similarly to our previous study, only one molecule equally responded to the two selection criteria defined (i.e., total cost of reimbursement and total amount of packs reimbursed) for four out of all 1st level ATC classes (the antineoplastic class L excepted). Thus, the same 20 molecules as in our previous study were selected. That is, class A: metformin, insulin glargine; class B: acetylsalicylic acid, rivaroxaban; class C: atorvastatin, rosuvastatin; class D: econazole, ciclopirox; class G: *Serenoa repens*, tamsulosine; class H:

prednisolone; class J: amoxicillin, pyostacine; class M: ibuprofen; class N: paracetamol; class P: ivermectin; class R: salbutamol, tiopropium; class S: cromolyn sodium, timolol (Table 1).

Statistical Analyses

Statistical analyses were computed using Jamovi Software© (open source software, Jonathon Love, University of Newcastle, University Dr, Callaghan NSW 2308, Australia).

We firstly calculated the amount of reimbursed DDD for a pack per precarious patient (P) and non-precarious patient (NP). Secondly, we computed the mean DDD for each molecule and for all packs.

To compare the GPs prescriptions between regions and populations for each of the 20 molecules selected, we computed repeated measures ANOVA with population (P and NP) and region (BR, CR, OSR, OCR) as factors (sphericity correction: Greenhouse-Geisser; Post-Hoc Tests, Bonferroni corrected).

Results

Although analyses were computed for each molecule separately (see above), we report below the results for all molecules pooled together for each ANOVAs level (i.e., effect of population, effect of region, population*region interaction).

Effect of Population on GPs prescriptions

DDD significantly differed between NP and P for 11 molecules: amoxicillin, ciclopirox, cromolyn sodium, econazole, ibuprofen, metformin, paracetamol, tamsulosine, timolol and tiopropium.

Mean DDD was significantly higher in P than NP for 8 out of these 11 molecules, i.e., amoxicillin, ciclopirox, cromolyn sodium, econazole, ibuprofen, tamsulosine, timolol, and tiopropium (Table 1).

Table 1 – Statistical comparisons computed on DDD for each molecule between precarious and non-precarious populations

Mean DDD for each molecule in each ATC class for each non-precarious and precarious population and statistical comparisons between groups are reported (**ATC** = anatomical therapeutic chemical; **DDD** = Defined Daily Dose; **NP** = non-precarious; **P** = precarious; **sd** = standard deviation; * indicates a significant effect (Bonferroni corrected)).

In contrast, mean DDD was significantly lower in P than NP for atorvastatin, metformin, and paracetamol (Table 1).

Effect of Region on GPs prescriptions

DDD significantly differed between regions for 11 molecules: amoxicillin, atorvastatin, ciclopirox, cromolyn sodium, econazole, ibuprofen, metformin, paracetamol, prednisolone, tamsulosine, and timolol

Class	Molecule	DDD (mean ± sd)		F	*P*-values $P_{Bonferroni}$
		NP	P		
A	metformin	0.074 ± 0.270	0.007 ± 0.025	$F_{(1,344)} = 33.6$	<0.001*
	insulin glargine	0.028 ± 0.077	0.002 ± 0.005	$F_{(1,9)} = 1.76$	0.217
B	acetylsalicylic acid	1.000 ± 2.100	0.071 ± 0.140	$F_{(1,13)} = 3.87$	0.071
	rivaroxaban	8.000 ± 1.300	1.400 ± 4.100	$F_{(1,17)} = 2.70$	0.146
C	atorvastatin	0.038 ± 0.120	0.004 ± 0.015	$F_{(1,390)} = 53.5$	<0.001*
	rosuvastatin	0.052 ± 0.150	0.082 ± 0.380	$F_{(1,43)} = 2.64$	0.119
D	econazole	0.000 ± 0.000	0.001 ± 0.003	$F_{(1,77)} = 17.1$	<0.001*
	ciclopirox	0.000 ± 0.000	0.000 ± 0.000	$F_{(1,29)} = 7.30$	0.011*
G	*Serenoa repens*	0.012 ± 0.042	0.140 ± 1.100	$F_{(1,50)} = 2.61$	0.113
	tamsulosine	0.012 ± 0.230	0.038 ± 0.140	$F_{(1,63)} = 9.65$	0.003*
H	prednisolone	0.022 ± 0.056	0.022 ± 0.057	$F_{(1,64)} = 0.423$	0.518
I	amoxicillin	0.003 ± 0.010	0.005 ± 0.140	$F_{(1,266)} = 39.9$	<0.001*
	pyostacine	0.052 ± 0.100	0.210 ± 0.600	$F_{(1,3)} = 1.32$	0.334
M	ibuprofen	0.011 ± 0.037	0.016 ± 0.056	$F_{(1,121)} = 12.85$	<0.001*
N	paracetamol	0.050 ± 0.230	0.037 ± 0.210	$F_{(1,264)} = 13.8$	<0.001*
P	ivermectin	0.005 ± 0.009	0.160 ± 0.031	$F_{(1,3)} = 1.29$	0.339
R	salbutamol	0.160 ± 0.730	1.200 ± 7.400	$F_{(1,43)} = 2.64$	0.111
	tiotropium	0.240 ± 0.330	0.350 ± 0.700	$F_{(1,5)} = 7.06$	0.045*
S	cromolyn sodium	0.000 ± 0.000	0.000 ± 0.003	$F_{(1,26)} = 8.28$	0.008*
	timolol	0.018 ± 0.058	0.096 ± 0.390	$F_{(1,69)} = 16.4$	<0.001*

(Table 2).

Table 2
Statistical comparisons computed on DDD for each molecule between regions

Class	Molecule	Region	DDD (mean ± sd)	F	*p*-values
A	metformin	BR	0.036 ± 0.146^{abd}	$F_{(1.18, 405.29)} = 29.2$	< 0.001*
		CR	0.062 ± 0.274^{aef}		
		OCR	0.042 ± 0.180^{ceg}		
		OSR	0.000 ± 0.000^{dfg}		
	insulin glargine			$F_{(1, 9)} = 1.74$	0.219
B	acetylsalicylic acid			$F_{(1.02, 13.20)} = 3.92$	0.068
	rivaroxaban			$F_{(1.01, 17.10)} = 2.92$	0.106
C	atorvastatin	BR	0.025 ± 0.090^{acd}	$F_{(1.37, 536.08)} = 44.3$	< 0.001*
		CR	0.031 ± 0.111^{bef}		
		OCR	0.023 ± 0.087^{ceg}		
		OSR	0.000 ± 0.000^{dfg}		
	rosuvastatin			$F_{(1.00, 43.01)} = 2.61$	0.114
D	econazole	BR	0.001 ± 0.002^{abd}	$F_{(1.33, 102.13)} = 15.4$	< 0.001*
		CR	0.001 ± 0.002^{aeg}		
		OCR	0.0201 ± 0.003^{cfh}		
		OSR	0.000 ± 0.000^{dgh}		
	ciclopirox	BR	0.002 ± 0.004^{ace}	$F_{(1.05, 30.53)} = 6.54$	0.015*
		CR	0.002 ± 0.005^{bfh}		
		OCR	0.031 ± 0.008^{dgj}		
		OSR	0.001 ± 0.000^{eij}		

Mean DDD for each molecule in each ATC class for each region and statistical comparisons between regions are reported (**ATC** = anatomical therapeutic chemical; **DDD** = Defined Daily Dose; **NP** = non-precarious; **P** = precarious; **sd** = standard deviation; * indicates a significant effect (Bonferroni corrected)).

Class	Molecule	Region	DDD (mean ± sd)	F	*p*-values
G	*Serenoa repens*			$F_{(1.00, 50.04)} = 2.58$	0.114
	tamsulosine	BR	0.008 ± 0.041^{ace}	$F_{(1.02, 64.30)} = 9.36$	0.003*
		CR	0.012 ± 0.047^{bfh}		
		OCR	0.012 ± 0.054^{dgi}		
		OSR	0.058 ± 0.526^{ehi}		
H	prednisolone	BR	0.008 ± 0.014^{ace}	$F_{(1.17, 74.86)} = 12.12$	< 0.001*
		CR	0.012 ± 0.002^{bfh}		
		OCR	0.012 ± 0.022^{dgi}		
		OSR	0.058 ± 0.193^{ehi}		
I	amoxicillin	BR	0.006 ± 0.014^{abc}	$F_{(1.48, 392.66)} = 35.4$	< 0.001*
		CR	0.005 ± 0.014^{adf}		
		OCR	0.004 ± 0.010^{beg}		
		OSR	0.003 ± 0.012^{cfg}		
	pyostacine			$F_{(3, 9)} = 1.31$	0.331
M	ibuprofen	BR	0.013 ± 0.038^{ace}	$F_{(1.32, 159.45)} = 11.46$	< 0.001*
		CR	0.017 ± 0.049^{bfh}		
		OCR	0.015 ± 0.047^{dgi}		
		OSR	0.059 ± 0.019^{ehi}		
N	paracetamol	BR	0.051 ± 0.196^{ace}	$F_{(1.15, 302.51)} = 12.5$	< 0.001*
		CR	0.061 ± 0.264^{bfh}		
		OCR	0.047 ± 0.262^{dgi}		

Mean DDD for each molecule in each ATC class for each region and statistical comparisons between regions are reported (**ATC** = anatomical therapeutic chemical; **DDD** = Defined Daily Dose; **NP** = non-precarious; **P** = precarious; **sd** = standard deviation; * indicates a significant effect (Bonferroni corrected)).

Class	Molecule	Region	DDD (mean ± sd)	F	*p*-values
		OSR	0.000 ± 0.000^{ehi}		
P	ivermectin			$F_{(3, 9)} = 1.30$	0.333
R	salbutamol			$F_{(1.00, 43.01)} = 2.61$	0.114
	tiotropium			$F_{(1.02, 5.08)} = 5.63$	0.063
S	cromolyn sodium	BR	0.004 ± 0.011^{ace}	$F_{(1.42, 36.93)} = 7.25$	0.005*
		CR	0.054 ± 0.013^{bfh}		
		OCR	0.005 ± 0.010^{dgi}		
		OSR	0.000 ± 0.000^{ehi}		
	timolol	BR	0.011 ± 0.041^{ace}	$F_{(1.00, 69.18)} = 16.2$	< 0.001*
		CR	0.015 ± 0.047^{bfh}		
		OCR	0.017 ± 0.054^{dgi}		
		OSR	0.168 ± 0.526^{ehi}		

Mean DDD for each molecule in each ATC class for each region and statistical comparisons between regions are reported (**ATC** = anatomical therapeutic chemical; **DDD** = Defined Daily Dose; **NP** = non-precarious; **P** = precarious; **sd** = standard deviation; * indicates a significant effect (Bonferroni corrected)).

Population*Region Interaction

There was a significant interaction between population and region for 11 molecules, i.e., amoxicillin, atorvastatin, ciclopirox, cromolyn sodium, econazole, ibuprofen, metformin, paracetamol, tamsulosine, timolol, and prednisolone (Table 1).

Table 3
Statistical comparisons computed on mean DDD between populations and regions

Class	Molecule	Region	DDD (mean ± sd)	DDD (mean ± sd)	F	*p*-values	Post-hoc $P_{Bonferroni}$ Comp. NP	Post-hoc $P_{Bonferroni}$ Comp. P
			NP	P				
A	metformin				$F_{(1.17, 401.51)} = 28.8$	< 0.001*		
		BR	0.065 ± 0.200	0.006 ± 0.020			< 0.001*	1.000
		CR	0.115 ± 0.380	0.010 ± 0.032				
		OCR	0.093 ± 0.270	0.010 ± 0.029			< 0.001*	1.000
		OSR	0.000 ± 0.000	0.000 ± 0.000				
	insulin glargine				$F_{(1.00, 9.00)} = 1.75$	0.219		
B	acetylsalicylic acid				$F_{(1.01, 13.17)} = 3.88$	0.070		
	rivaroxaban				$F_{(1.01, 17.10)} = 2.92$	0.106		
C	atorvastatin				$F_{(1.34, 522.27)} = 46.3$	< 0.001*		

The results of repeated measures ANOVAS with populations and regions as factors are reported. Only the comparisons between regions with similar prevalence are reported (i.e., BR vs. CR; OCR vs. OSR) (**ATC** = anatomical therapeutic chemical; **BR** = Brittany Region; **CR** = Center Region; **DDD** = defined daily dose; **NP** = non-precarious; **OCR** = Occitany Region; **OSR** = Overseas Regions; **P** = precarious; **sd** = standard deviation; * indicates a significant effect (Bonferroni corrected)).

Class	Molecule	Region	DDD (mean ± sd)	DDD (mean ± sd)	F	*p*-values	Post-hoc $P_{Bonferroni}$ Comp. NP	Post-hoc $P_{Bonferroni}$ Comp. P
		BR	0.045 ± 0.120	0.005 ± 0.016			0.062	1.000
		CR	0.056 ± 0.150	0.006 ± 0.019				
		OCR	0.000 ± 0.000	0.000 ± 0.000			< 0.001*	1.000
		OSR	0.000 ± 0.000	0.000 ± 0.000				
	rosuvastatin				$F_{(3, 9)} = 1.31$	0.331		
D	econazole				$F_{(1.35, 104.17)} = 13.4$	< 0.001*		
		BR	0.000 ± 0.000	0.001 ± 0.003			1.000	1.000
		CR	0.000 ± 0.000	0.001 ± 0.002				
		OCR	0.000 ± 0.001	0.002 ± 0.003			1.000	< 0.001*
		OSR	0.000 ± 0.001	0.000 ± 0.000				
	ciclopirox				$F_{(1.04, 30.28)} = 5.95$	0.020*		

The results of repeated measures ANOVAS with populations and regions as factors are reported. Only the comparisons between regions with similar prevalence are reported (i.e., BR vs. CR; OCR vs. OSR) (**ATC** = anatomical therapeutic chemical; **BR** = Brittany Region; **CR** = Center Region; **DDD** = defined daily dose; **NP** = non-precarious; **OCR** = Occitany Region; **OSR** = Overseas Regions; **P** = precarious; **sd** = standard deviation; * indicates a significant effect (Bonferroni corrected)).

Class	Molecule	Region	DDD (mean ± sd)	DDD (mean ± sd)	F	*p*-values	Post-hoc $P_{Bonferroni}$ Comp. NP	Post-hoc $P_{Bonferroni}$ Comp. P
		BR	0.001 ± 0.001	0.003 ± 0.005			1.000	1.000
		CR	0.001 ± 0.001	0.004 ± 0.006				
		OCR	0.001 ± 0.002	0.005 ± 0.012			1.000	< 0.001*
		OSR	0.000 ± 0.000	0.000 ± 0.000				
G	*Serenoa repens*				$F_{(1.00, 50.00)} = 2.71$	0.106		
	tamsulosine				$F_{(1.00, 63.09)} = 13.8$	< 0.001*		
		BR	0.011 ± 0.018	0.005 ± 0.009			1.000	1.000
		CR	0.017 ± 0.018	0.008 ± 0.016				
		OCR	0.016 ± 0.027	0.009 ± 0.016			1.000	< 0.001*
		OSR	0.000 ± 0.000	0.150 ± 0.290				
H	prednisolone				$F_{(2.21, 141.30)} = 12.1$	< 0.001*		

The results of repeated measures ANOVAS with populations and regions as factors are reported. Only the comparisons between regions with similar prevalence are reported (i.e., BR vs. CR; OCR vs. OSR) (**ATC** = anatomical therapeutic chemical; **BR** = Brittany Region; **CR** = Center Region; **DDD** = defined daily dose; **NP** = non-precarious; **OCR** = Occitany Region; **OSR** = Overseas Regions; **P** = precarious; **sd** = standard deviation; * indicates a significant effect (Bonferroni corrected)).

Class	Molecule	Region	DDD (mean ± sd)	DDD (mean ± sd)	F	*p*-values	Post-hoc $P_{Bonferroni}$ Comp. NP	Post-hoc $P_{Bonferroni}$ Comp. P
		BR	0.027 ± 0.062	0.0312 ± 0.066			1.000	1.000
		CR	0.022 ± 0.045	0.019 ± 0.038				
		OCR	0.036 ± 0.077	0.037 ± 0.080			< 0.001*	< 0.001*
		OSR	0.000 ± 0.000	0.000 ± 0.000				
I	amoxicillin				$F_{(1.85, 491.88)} = 28.8$	< 0.001*		
		BR	0.004 ± 0.012	0.007 ± 0.016			1.000	1.000
		CR	0.004 ± 0.012	0.007 ± 0.016				
		OCR	0.004 ± 0.011	0.006 ± 0.015			< 0.001*	< 0.001*
		OSR	0.004 ± 0.012	0.000 ± 0.000				
	pyostacine				$F_{(3, 9)} = 1.31$	0.331		
M	ibuprofen				$F_{(1.32, 159.45)} = 11.46$	< 0.001*		

The results of repeated measures ANOVAS with populations and regions as factors are reported. Only the comparisons between regions with similar prevalence are reported (i.e., BR vs. CR; OCR vs. OSR) (**ATC** = anatomical therapeutic chemical; **BR** = Brittany Region; **CR** = Center Region; **DDD** = defined daily dose; **NP** = non-precarious; **OCR** = Occitany Region; **OSR** = Overseas Regions; **P** = precarious; **sd** = standard deviation; * indicates a significant effect (Bonferroni corrected)).

Class	Molecule	Region	DDD (mean ± sd)	DDD (mean ± sd)	F	*p*-values	Post-hoc $P_{Bonferroni}$ Comp. NP	Post-hoc $P_{Bonferroni}$ Comp. P
		BR	0.010 ± 0.029	0.017 ± 0.045			1.000	1.000
		CR	0.015 ± 0.042	0.019 ± 0.055				
		OCR	0.018 ± 0.051	0.027 ± 0.083			< 0.001*	< 0.001*
		OSR	0.000 ± 0.000	0.000 ± 0.000				
N	paracetamol				$F_{(1.66, 438.62)} = 11.9$	< 0.001*		
		BR	0.060 ± 0.022	0.042 ± 0.170			1.000	1.000
		CR	0.072 ± 0.028	0.052 ± 0.250				
		OCR	0.061 ± 0.027	0.051 ± 0.270			< 0.001*	< 0.001*
		OSR	0.000 ± 0.000	0.000 ± 0.000				
P	ivermectin				$F_{(3.00, 9.00)} = 1.28$	0.338		
R	salbutamol				$F_{(1.00, 43.00)} = 2.64$	0.112		

The results of repeated measures ANOVAS with populations and regions as factors are reported. Only the comparisons between regions with similar prevalence are reported (i.e., BR vs. CR; OCR vs. OSR) (**ATC** = anatomical therapeutic chemical; **BR** = Brittany Region; **CR** = Center Region; **DDD** = defined daily dose; **NP** = non-precarious; **OCR** = Occitany Region; **OSR** = Overseas Regions; **P** = precarious; **sd** = standard deviation; * indicates a significant effect (Bonferroni corrected)).

Class	Molecule	Region	DDD (mean ± sd)	DDD (mean ± sd)	F	*p*-values	Post-hoc $P_{Bonferroni}$ Comp. NP	Post-hoc $P_{Bonferroni}$ Comp. P
	tiotropium				$F_{(1.00, 5.00)} = 5.21$	0.071		
S	cromolyn sodium				$F_{(1.47, 38.30)} = 6.48$	0.008*		
		BR	0.001 ± 0.002	0.007 ± 0.015			1.000	1.000
		CR	0.002 ± 0.003	0.009 ± 0.018				
		OCR	0.002 ± 0.003	0.009 ± 0.014			1.000	< 0.001*
		OSR	0.000 ± 0.000	0.000 ± 0.000				
	timolol				$F_{(1.00, 69.03)} = 15.6$	< 0.001*		
		BR	0.018 ± 0.056	0.005 ± 0.015			1.000	1.000
		CR	0.023 ± 0.062	0.008 ± 0.022				
		OCR	0.028 ± 0.075	0.009 ± 0.023			1.000	< 0.001*
		OSR	0.000 ± 0.000	0.412 ± 0.760				

The results of repeated measures ANOVAS with populations and regions as factors are reported. Only the comparisons between regions with similar prevalence are reported (i.e., BR vs. CR; OCR vs. OSR) (**ATC** = anatomical therapeutic chemical; **BR** = Brittany Region; **CR** = Center Region; **DDD** = defined daily dose; **NP** = non-precarious; **OCR** = Occitany Region; **OSR** = Overseas Regions; **P** = precarious; **sd** = standard deviation; * indicates a significant effect (Bonferroni corrected)).

For tamsulosine and timolol, *post hoc* tests indicated that this interaction was attributable to higher DDD in OSR precarious populations. In contrast, DDD was significantly lower in OSR precarious populations compared to OCR, BR and CR precarious populations for the 7 remaining molecules, i.e., amoxicillin, ciclopirox, cromolyn sodium, econazole, ibuprofen, prednisolone, and paracetamol (Table 3).

Discussion

We investigated whether high and daily exposure of GPs to precariousness increases the inequality of prescriptions between non-precarious and precarious populations. Using the same pharmaco-epidemiological approach as in our previous national study [5], we focused our analyses on four French regional populations with respectively low (BR, CR) and high (OSR, OCR) precariousness prevalence. We assumed that there are more inequalities in prescriptions of GPs who are more highly and daily exposed to precariousness (OSR, OCR) compared to GPs who are less exposed to precariousness (BR, CR). Our findings confirmed our working hypothesis.

Replicating our national study, we firstly report that the amount of reimbursed drugs prescriptions significantly differed between populations. This was the case for 11 out of all 20 tested molecules, i.e., amoxicillin, ciclopirox, cromolyn sodium, econazole, ibuprofen, metformin, paracetamol, tamsulosine, timolol, and tiopropium. Secondly, we observe that reimbursed drugs prescriptions also significantly differed between regions with respectively low and high precariousness prevalence. In addition to atorvastatin and prednisolone, this effect also concerned amoxicillin, ciclopirox, cromolyn sodium, econazole, ibuprofen, metformin, paracetamol, tamsulosine, and timolol.

This effects overlap was confirmed at the level of the population*region interaction for 9 of the above-mentioned molecules showing combined effects of population and region (i.e., amoxicillin, ciclopirox, cromolyn sodium, econazole, ibuprofen, metformin, paracetamol, tamsulosine, and timolol) and 2 further molecules (i.e., atorvastatin and prednisolone). *Post hoc* tests showed that tamsulosine and timolol were significantly over-reimbursed in OSR precarious populations, compared to OCR, BR, and CR precarious populations. The remaining 9 molecules were under-reimbursed in this same population. In line with our previous study [5], there was more drugs that were under- (n = 7) than over-reimbursed (n = 2).

Regarding over-reimbursed molecules, tamsulosine and timolol indications target chronic diseases. Tamsulosine, as an alpha-blocker, is used to reduce low urinary tract symptoms (LUTS) in men with benign prostate hypertrophy [15]. Timolol, as a beta-blocker, is indicated for open-angle glaucoma [16], known to more frequently affect older men and older people, respectively. However, it is well-documented that there are more female than male CMU-beneficiaries. Although the percentages of women and men is equally distributed in the 20-60-year bracket of the French general population, female CMU-beneficiaries account for 58% of the 20-40-year bracket, 54% of the 40-60-year bracket and 53% of the over-60-years-olds [17]. Furthermore, CMU-beneficiaries are younger, compared to the general population. 44% of CMU-beneficiaries are under 20 years of age and half are adults from 20 to 59. This significantly contrasts with the general population, equally distributing across the four standard age brackets. Accordingly,

tamsulosine and timolol in our study should have been less prescribed in regions with high precariousness prevalence, especially in OSR, which was not the case.

Regarding LUTS, a Cameroonian study demonstrated that the frequency of the disease is significantly higher in Black African people, compared to White American or Japanese people [18]. The severity of LUTS symptoms also tended to be higher in Black African patients [19]. Overseas populations (OSR) are mostly Black African descendants (e.g., Guyana: 40%; Martinique: 75%; Reunion: 35%). At first sight, these findings by Fouda et al may explain the over-reimbursement of tamsulosine in OSR in our study. However, these do not account for its over-reimbursement in OSR precarious populations in particular. Moreover, the French College of Urology (FCU) reports that there is neither correlation nor association between LUTS and ethnicity [17]. The fact that no further study replicated the findings by Fouda et al tends to also confirm the FCU report. Moreover, epidemiological studies [8, 19] showed that the risk for developing LUTS does not differ between precarious and non-precarious populations.

The risk factor for open-angle glaucoma has been reported to correlate with ethnicity but not with precariousness [20]. However, in our study, the over-reimbursement of timolol only concerns OSR precarious populations, invalidating the hypothesis that this over-reimbursement is due to ethnical characteristics.

We assume that our present results on tamsulosine and timolol cannot be explained by epidemiological nor ethnical factors but rather by inequalities in access to health care for precarious populations, especially in regions with high precariousness prevalence. Indeed, a promising alternative to pharmacological treatments in both benign prostate hypertrophy and open-angle glaucoma is laser surgery. Precarious populations cannot afford these additional costs. It suggests that the over-reimbursed prescriptions of tamsulosine and timolol reflect a failure of the health system to compensate for inequalities in access to care and cannot be considered a deleterious effect of higher and daily exposure of GPs to precariousness *per se*. Thus, our data regarding over-reimbursed drugs prescriptions do not verify our working hypothesis. It is not the case for under-reimbursed prescriptions as discussed below.

Molecules that were found to be under-reimbursed usually target acute pathologies. This concerned econazole, ciclopirox, prednisolone, amoxicillin, ibuprofen, paracetamol, and cromolyn sodium. These results significantly contrast with our national study [5] in which econazole and ciclopirox were more reimbursed and paracetamol less reimbursed in precarious populations, and prednisolone, amoxicillin, ibuprofen, and cromolyn-sodium did not differ between populations. It is worth noting that access to the ISPL database (see Methods) only provides with aggregated data on amounts reimbursed per pack. It means that extracting data relative to the patients' age, gender, health status, and underlying medical conditions is not possible. It is also the case for data relative to the precariousness prevalence, i.e., data informing whether each GP is exposed to high or low precariousness prevalence. Thus, it means that, in our national study, the effect of higher and daily exposure to precariousness on GPs prescriptions, i.e., on GPs working in regions with high precariousness prevalence, was probably smoothed, if not erased, by data collected from regions with low or balanced precariousness prevalence. The present regional study

was set up to overcome this shortcoming. Accordingly, the differences regarding drugs prescriptions observed between our two studies highlight that understanding in more definite way inequalities in access to health care requires *a priori* determining test-regions on the basis of their precariousness prevalence at the methodological level.

Below, we demonstrate how the under-reimbursement of drugs targeting acute pathologies in precarious populations reflects the negative impact of higher and more regular exposure to precariousness on GPs prescriptions. Amoxicillin was found to be less prescribed in precarious populations living in regions with high precarious prevalence (OSR/OCR) than in precarious populations living in regions with low precariousness prevalence (BR/CR). This effect was further greater in OSR than OCR. These findings are striking as the frequency of infections is well-documented to be higher in precarious populations compared to the general population [5]. The inappropriate prescriptions of antibiotics (over-prescription or second-line antibiotics which are prescribed directly from the start) has been shown to prevail in precarious people, regardless of the precariousness indicators, i.e., education level [21, 22], income [22], geographical origin, health cover [23], unemployment, or single-parent family [24]. In general, precariousness fosters antibiotics misuse, such as self-medication or use of “leftover” antibiotics [25]. WHO stated that poverty is one of the main factors driving resistance to antimicrobials. Some GPs – and probably those who are not daily exposed to precariousness – are not necessarily aware of the low level of literacy in precarious population [26] that potentially leads these patients to misuse antibiotics, and, thus, to significant differences in consumptions compared to the general population. However, resistance to antimicrobials also probably relates to the under-prescription of these same antimicrobials in precarious populations [5].In our national study, amoxicillin was found to be equally prescribed between groups. Hence, our present regional results confirm that aggregated data tend to smooth differences between tested populations at the national level, not only between precarious and non-precarious individuals but also between precarious populations in region with high and low precariousness prevalence.

Similarly to amoxicillin, econazole and ciclopirox were also significantly under-prescribed. These two molecules target dermatological diseases such as mycoses. According to several authors [27, 28], dermatological conditions are the most common health problem in precarious populations, especially in homeless people, because of difficult living conditions (poor hygiene, overcrowding, nutritional deficiencies, unfavorable working conditions etc.). Strengthening these observations, over-prescription of antifungals has been largely reported in precarious individuals, especially in children [28]. Consequently, an over-prescription of econazole and ciclopirox should have been observed in OSR and OCR precarious populations. In our previous work, these molecules were found to be over-reimbursed. Again, this difference observed between our present and previous work reinforces the hypothesis of an effect of data aggregation. It is plausible that the prescriptions of econazole and ciclopirox to precarious population in regions with low precariousness prevalence impacted our general findings in our national study.

Hence, we here show that the under-prescription of amoxicillin, econazole and ciclopirox in precarious populations living in regions with high precariousness prevalence cannot be explained by epidemiological

or ethical factors, neither by the failure of the health system to compensate for inequalities. We rather suggest that this under-prescription reflects the exhaustion of GPs who are more exposed to precariousness, negatively impacting the quality of care (as discussed below). The same hypothesis is probably suitable regarding prednisolone, paracetamol, cromolyn sodium, and ibuprofen. However, this hypothesis needs to be considered with caution as the various therapeutic indications for these four molecules render difficult to delimitate which disease has been targeted on the only basis of the aggregated ISPL data.

Considered collectively, our findings show that the French free health care cover fails to compensate for inequalities, confirming our previous study [5]. This is reflected in over-reimbursed drugs prescriptions (tamsulosine, timolol). Our results also suggest that under-prescriptions (amoxicillin, econazole, ciclopirox) not only reveal this failure for compensating inequalities but also the negative impact of a higher and daily exposure to precariousness on GPs prescriptions (i.e., in OSR and OCR). As mentioned in the introduction, precarious populations are more difficult to care for [9]. It is firstly due to low rates of literacy and language difficulties but also to significant comorbidities in these populations, causing an extra workload and an increased psychical investment, potentially exhausting GPs. Secondly, precarious populations adhere less easily to treatment and hospitalization. This low compliance necessitates caregivers to significantly focus on patient education, which is also an important cause of exhaustion. Thirdly, because of their difficult socio-economic conditions, precarious patients tend to neglect their own health status, also increasing the GPs investment on time and psychical resources. Taken together, the attempt to compensate for these encountered difficulties generates a considerable loss of energy in GPs which, as a consequence, is associated with a lack of positive feedback and a diminished personal accomplishment. Under normal conditions, workload in medical care is counterbalanced by the patients' positive attitude towards their GPs, their adherence to treatment, their health improvement or recovery, and, thus, by an acquired personal satisfaction.

On the basis of a previous neuro-phenomenological work [10], we here postulate that exhausting working conditions due to exposure to precariousness impairs empathic skills in GPs, leading to burnout, which negatively impacts the quality of care. Indeed, the alteration of empathy is considered a non-negligible risk factor for burnout in medical care [10, 12]. Empathy (feeling into) is a multidimensional skill consisting in feeling and understanding the lived experience of another individual and his/her associated mental state while adopting his/her visuo-spatial and psychological perspective and consciously maintaining self-other distinction [29–33]. This complex phenomenon includes various and cooperating automatic, emotional, cognitive, visuo-spatial and self-regulatory processes [29 – 3]. At the neuro-functional level, these are sustained by the integration of balanced activations in largely distributed and functionally distinct brain networks [30, 33], notably in the mirror neuron system (MNS), mentalizing network (MENT), executive, emotional and vestibular systems. In contrast, hyper-activations in the MNS and emotional system associated with decreased activations in the MENT, executive and vestibular systems trigger sympathetic reactions towards others [33]. When sympathizing (feeling with), individuals are feeling the same thing as others are feeling [34] and at the same time [35], tending to merge identities. We assume that a high and long lasting exposure to precariousness leads GPs to sympathize with their

precarious patients instead of empathizing. It generates a hyper-recruitment of the MNS and emotional system and leads to emotional exhaustion which is the first symptom of burnout [36]. Then, we further posit that GPs, in order to alleviate distress and respond to this emotional exhaustion, develop a copying strategy leading them to keep away from their patients. Depersonalization is the second symptom of burnout and consists of negative, distant and/or impersonal attitudes towards patients, leading to isolation and rejection [36]. Hence, repeated exposures to difficult situations encountered with precarious populations and repeated experiences of failures triggers a complete breakdown of empathy, causing burnout syndrome in GPs and impacting negatively their prescriptions.

Conclusions

Using a pharmaco-epidemiological approach based on DDD modulations, we showed that a more highly and daily exposure of GPs to precariousness negatively impacts their prescriptions, reinforcing inequalities between precarious and non-precarious populations. This was reflected in under-reimbursed drugs in precarious populations targeting pathologies that are more encountered in these populations due to epidemiological factors. At the methodological level, we further demonstrated that understanding in more definite way inequalities in access to health care requires *a priori* determining test-regions on the basis of their precariousness prevalence. We assumed that exhausting working conditions, repeated exposures to difficult living conditions, and repeated experiences of failure impairs empathic skills in GPs, leading to burnout. Especially, depersonalization, i.e., a copying strategy in GPs suffering from burnout, triggers distant attitudes towards patients. This probably negatively impacts the quality of care and, thus, prescriptions. New pharmaco-epidemiological studies combining both clinical and neuro-functional investigations are needed to better explore the link between alteration of empathy, burnout and unequal prescriptions in GPs exposed to high precariousness. This is a challenging issue, notably in the current pandemic context in which physicians and healthcare professionals are significantly exhausted and precariousness dramatically worsens.

Abbreviations

ATC = Anatomical Therapeutic Chemical; **BR** = Brittany Region; **CMU** = Universal Medical Coverage; **CR** = Center Region; **DDD** = Defined Daily Dose; **FCU** = French College of Urology; **GP** = general practitioner; **ISPL** = Institut Statistique des Professionnels Libéraux; **LUTS** = low urinary tract symptoms; **MENT** = mentalizing network; **MNS** = mirror neuron systems; **NP** = non-precarious population; **OCR** = Occitany Region; **OSR** = Overseas Region; **P** = precarious population; **WHO** = World Health Organization

Declarations

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Consent for publication: Not applicable

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