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Article

General Practitioner-Related Factors Associated with Antibiotic Prescription in Community-Dwelling Adult Population

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Abstract: Background: The extensive use of antibiotics has contributed to the development of antibiotic resistance. Understanding the factors behind the attitude of physicians in prescribing antibiotics may be useful to address educational interventions to sensitize them to a more rational use of these drugs. This study aimed to evaluate the general practitioners' (GPs) characteristics potentially associated with antibiotic prescription in community-dwelling adults from 2000 to 2019. **Method:** Multivariable linear regression models were performed to evaluate the association of GPs' characteristics with the mean number of different antibiotics prescribed and the mean number of Defined Daily Doses (DDD) prescribed per patient. **Results:** We found that GPs older than 60 years prescribed a smaller number of different antibiotics per patient compared to 30–40 years old GPs (mean (standard error) 1.4 (0.5) vs. 1.8 (0.4)). In contrast older GPs prescribed more DDD compared to younger ones (28.9 (0.1) vs. 27.3 (0.3)). GPs prescribed 29 (0.1) DDD for >200 patients on polypharmacy vs. 28 (0.1) DDD for <100 patients on polypharmacy. The mean number of DDD prescribed increased by 5 units and by 16 units for each refill and switch, respectively. **Conclusions:** Age and number of patients in polypharmacy in charge were found to be associated with higher antibiotic prescriptions. The knowledge of the GPs-related factors could allow the stakeholders to design interventions to sensitize them to a more appropriate use of antibiotics in view of the increasing issue of antibiotic resistance.

Keywords: antibiotics; elderly; physician-related factors; general physicians

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1. Introduction

The extensive use of antibiotics has contributed to the development of antibiotic resistance, which is currently one of the major issues of global public health [1]. Lack and/or loss of therapeutic efficacy of the available antibiotics, due to antibiotic resistance might have a great impact on the health system, both for increased mortality related to resistant infections and for increased healthcare and social costs [2]. In addition to antimicrobial resistance, the over and inappropriate use of antibiotics can cause adverse clinical outcomes [3]. Several studies have shown that, often, antibiotics prescribed by general practitioners (GPs) and physicians of emergency care units are unnecessary [4]. In 2017, the Italian Government, in agreement with the Regions adopted the first National Action Plan against Antimicrobial Resistance (PNCAR) 2017–2020 [5] involving both the stakeholders and citizens to face increasing resistance and spread of antibiotic-resistant microorganisms. Despite the downward trend from 2013 to 2019, in Italy, antibiotic consumption continues to be above the European average with a consumption of 19.8 Defined Daily Doses (DDD) per 1000 inhabitants per day, compared to the 18.0 DDD per 1000 inhabitants per day of the EU countries [2].

In order to develop effective strategies for a more rational use of antibiotics in ambulatory care, a better understanding of factors influencing GPs' prescribing behavior is essential. Among clinicians' characteristics: age [6], sex [6–10], number of patients under care [9,11–15], time in practice [10,13,16], and location of work [9,11,14] were found to be associated with antibiotic prescribing in community-dwelling adults. Moreover, scarce knowledge and awareness about possible risks related to drug use and their interaction, especially for antibiotics, both by physicians and patients, access to antibiotics without prescription and leftover antibiotics from earlier prescriptions, inadequate medical training, pharmaceutical promotion, lack of rapid diagnostic tests and patient-doctor interaction (complacency towards patients' expectations or fear of possible future complications in the patients) were found to be the major factors driving to irrational use of antibiotics [7,12,16–18].

These findings reveal that antibiotic prescribing is a complex process influenced by factors affecting all the actors involved, including physicians, healthcare systems, and patients and such factors are mutually dependent.

In our previous studies, we assessed the patient-related characteristics associated with the prescription of antibiotics in Italian adults, founding that older age, female sex, polypharmacy, and hospital admissions were the main factors associated to be prescribed at least one antibiotic drug [19,20].

Based on these results, this study aimed to assess the General Practitioners' (GPs) related factors possibly associated with higher antibiotic prescriptions in a large Italian adult population, living in the Lombardy region (Northern Italy) from 2000 to 2019.

2. Results

2.1. Characteristics of Physicians Working for NHS between 2000 and 2019

During 2000, 7238 GPs with a mean age (std.dev) of 47.2 (7.6) years worked for the Regional Healthcare Service. Between 2000 and 2018, 2494 physicians with a mean age (std.dev) of 59.3 (3.2) years left the Lombardy region health service, while 1913 with a mean age (std.dev) of 54.9 (3.1) entered. Details by years of the turnover of GPs in the Regional Healthcare Service are reported in Figure 1. At the beginning of the study, the mean age of physicians was 47 years, and increased up to 60 years old in 2019 (Table 1). Male physicians' proportion slightly decreased from 72% in 2000 to 62% in 2019.

Table 1. Characteristics of general physicians (GPs) in the Lombardy Region from 2000 to 2019.

Characteristic	Index Year 2000 N = 7238	 2010 N = 6779	 2018 N = 6801	 2019 N = 6657
Age, years, mean (SD)	47.2 (7.6)	54.6 (5.8)	59.3 (7.9)	59.8 (8.2)
Age groups, years, n (%)				
30–40	1181 (16.3)	84 (1.2)	352 (5.2)	372 (5.6)
41–50	4392 (60.7)	1456 (21.5)	403 (5.9)	382 (5.7)
51–60	1063 (14.7)	4347 (64.1)	2313 (34.0)	2018 (30.3)
>60	601 (8.3)	892 (13.2)	3733 (54.9)	3885 (58.4)
Sex, Male, n (%)	5208 (72.0)	4619 (68.1)	4305 (63.3)	4156 (62.4)
LHU, n (%)				
Milano City	2631 (36.4)	2340 (34.5)	2376 (34.9)	2334 (35.1)
Insubria	1042 (14.4)	994 (14.7)	989 (14.5)	982 (14.7)
Montagna	260 (3.6)	245 (3.6)	216 (3.2)	186 (2.8)
Brianza	846 (11.7)	779 (11.5)	785 (11.5)	768 (11.5)
Bergamo	745 (10.3)	730 (10.8)	717 (10.5)	709 (10.6)
Brescia	737 (10.2)	731 (10.8)	764 (11.2)	738 (11.1)
Val Padana	564 (7.8)	536 (7.9)	534 (7.9)	532 (8.0)
Pavia	413 (5.6)	424 (6.2)	420 (6.3)	408 (6.2)
Patients in charge, median (IQR range)	706 (457–841)	902 (683–1006)	995 (778–1078)	1043 (820–1122)

Table 1. *Cont.*

Characteristic	Index Year			
	2000 N = 7238	**2010 N = 6779**	**2018 N = 6801**	**2019 N = 6657**
Proportion of older patients, median (IQR range)	33.4 (28.1–38.5)	35.0 (30.2–39.3)	37.1 (32.1–41.0)	36.9 (31.5–40.8)
Proportion of patients on polypharmacy, median (IQR range)	17.5 (13.9–21.5)	24.0 (19.8–28.1)	26.1 (21.1–30.6)	25.1 (20.3–29.8)
Mean number of different antibiotics prescribed per patient in the year, median (IQR range)	1.9 (1.8–2.1)	1.9 (1.8–2.1)	1.3 (1.2–1.3)	1.8 (1.7–1.9)
The mean number of DDD of antibiotics prescribed per patient in the years, median (IQR range)	40.2 (34.5–47.0)	21.2 (13.3–26.0)	24.2 (20.6–28.5)	32.2 (25.2–37.8)
Number of antibiotic refills for a month per patient, median (IQR range)	1.3 (1.2–1.5)	1.2 (0–1.4)	1.3 (1.2–1.5)	1.3 (1.1–1.5)
Number of antibiotic switches for a month per patient, median (IQR range)	1.2 (1.1–1.3)	1.1 (0–1.2)	1.1 (1.1–1.2)	1.1 (1.0–1.2)

SD: Standard Deviation; LHU: Local Health Unit; IQR: Inter Quartile Range; DDD: Defined Daily Dose.

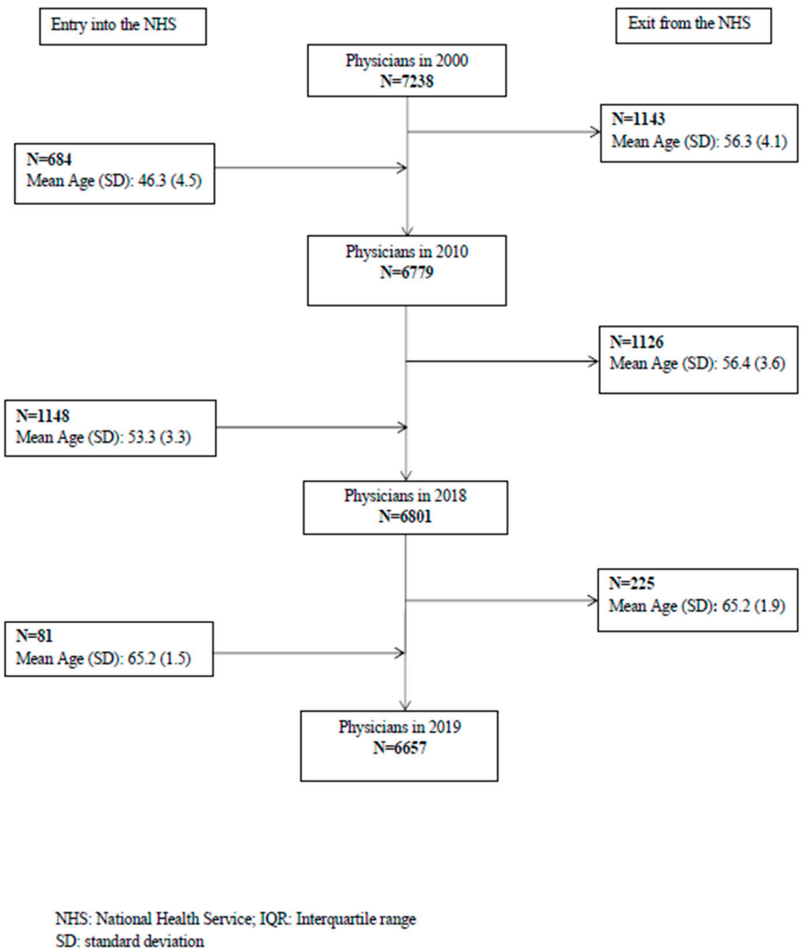

Figure 1. Flowchart of general physicians' (GPs) new entries and drop-outs in Lombardy National Health Service (NHS) from 2000 to 2019.

As a consequence, the total number of adult patients in charge per GP slightly increased, as well as the prevalence of older patients (from 33% in 2000 to 37% in 2018) and of those exposed to polypharmacy (from 17.5% in 2000 to 25% in 2019). The mean number of different antibiotics prescribed per patient in the year decreased from 2010 to 2018 but then increased again in 2019. The mean number of DDD antibiotics prescribed per patient each year fell by half from 2000 to 2010 and then increased in 2019.

Geographical distributions of GPs characteristics are presented in Table S1.

2.2. GP-Related Factors and Antibiotic Prescription

Table 2 reports the results of the two multivariable regression models to assess GP-related factors associated with the mean number of different antibiotics and the number of DDD prescribed per patient in the year. Older GPs prescribed a higher number of DDD with respect to the youngest, but they prescribed a lower number of different antibiotics. Male GPs prescribed a lower number of different antibiotics per patient with respect to female GPs. In the LHU of Brescia, GPs prescribed more different antibiotics than in the LHU of Milan. The biggest reduction in the number of DDD and different antibiotics prescribed was in 2010 with a slight increase in the last years.

Having more than 200 patients on polypharmacy in charge was associated both with a higher number of different antibiotic prescriptions and the number of DDD prescribed per patient. The mean number of antibiotic refills and antibiotic switches did affect the number of DDDs prescribed per patient: in particular, the number of DDD prescribed increased by 5 units for each refill and by 16 units for each antibiotic switch.

Table 2. Results from multivariable regression models to assess General Practitioner (GPs)-related factors associated with antibiotic prescription.

	Number of Different Antibiotics Prescribed		**Number of DDD Prescribed**	
	Beta (95% CI)	***p*-Value**	**Beta (95% CI)**	***p*-Value**
Intercept	1.67 (1.64–1.70)	<0.0001	15.85 (15.20–16.50)	<0.0001
Age groups				
30–40	0		0	
41–50	−0.10 (−0.11; −0.08)	<0.0001	1.08 (0.52; 1.63)	0.0001
51–60	−0.02 (−0.04; −0.12)	0.0001	0.42 (0.13; 0.71)	0.0042
>60	−0.08 (−0.09; −0.07)	<0.0001	0.86 (0.63; 1.09)	<0.0001
Male	−0.02 (−0.03; −0.01)	0.0012	−0.26 (−0.52; 0.001)	0.0516
LHU				
Milano City	0		0	
Insubria	0.02 (0.01–0.04)	0.0052	0.04 (−0.33; 0.42)	0.8219
Montagna	0.01 (0.04; 0.09)	<0.0001	−1.16 (−1.84; −0.48)	0.0009
Brianza	0.03 (0.24; 0.05)	<0.0001	−0.26 (−0.68; 0.16)	0.2251
Bergamo	0.05 (0.39; 0.70)	<0.0001	−0.47 (−0.90; −0.30)	0.0360
Brescia	0.14 (0.12–0.16)	<0.0001	−0.76 (−1.17; −0.34)	0.0003
Val Padana	−0.01 (−0.03–0.01)	0.2911	−2.43 (−2.86; −1.99)	<0.0001
Pavia	0.06 (0.04; 0.87)	<0.0001	−1.09 (−1.64; −0.55)	0.0001
Year				
2000	0		0	
2010	−0.06 (−0.08; −0.04)	<0.0001	−17.04 (−17.38; −16.69)	<0.0001
2018	−0.73 (−0.75; −0.72)	<0.0001	0.16 (−0.08; 0.40)	0.1960
2019	0.50 (0.49; 0.51)	<0.0001	7.03 (6.82; 7.23)	<0.0001

Table 2. *Cont.*

	Beta (95% CI)	p-Value	Beta (95% CI)	p-Value
Number of subjects on polypharmacy in charge				
<100	0		0	
100–200	0.30 (0.28; 0.32)	<0.0001	−0.03 (−0.37; 0.32)	0.8793
>200	0.14 (0.13; 0.15)	<0.0001	1.02 (0.78; 1.26)	<0.0001
Number of antibiotic refills in a month	0.06 (0.04; 0.07)	<0.0001	4.46 (2.42; 6.50)	<0.0001
Number of antibiotic switches in a month	0.05 (0.02; 0.07)	0.0002	15.85 (13.67; 18.03)	<0.0001

Abbreviations: DDD: Defined Daily Dose; CI: Confidence Interval; LHU: Local Health Unit.

3. Discussion

3.1. Principal Findings

This study explored the GPs’ characteristics possibly affecting their antibiotic prescribing behaviour. We found that the major predictors of antibiotic prescription, both in terms of different antibiotics and DDD prescribed, were older age, a high number of patients on polypharmacy in charge, and antibiotic switches within a month. In particular, older physicians prescribed more antibiotics in terms of the number of DDD, but a smaller number of different antibiotics. This is probably due to the clinical experience gained over the years, with more awareness about the risk of inappropriate drug prescriptions. This is an important result, because the continuous changes in the antibiotics prescribed may be one of the causes of antibiotic resistance. Moreover, we found that as the number of antibiotic switches in a month increased, also the number of DDD of antibiotics prescribed increased. For each switch of antibiotics, the number of DDD increased by 16 units, corresponding to about two weeks. Other reasons for antibiotic switches or refill could be adverse reactions, re-infections, and tolerance issues, but the administrative nature of the database does not allow us to investigate this aspect.

The characteristics of physicians operating in the Lombardy Region significantly changed from 2000 to 2019. A big number of physicians left the NHS from 2000 to 2018. The new physicians entering the NHS in 2018 could not compensate for the drop out of the previous years. Moreover, older physicians entered the NHS, so the age group composition was going to become strongly unbalanced toward the older age groups in recent years. This is an alarming signal because the retirement of the older physicians not compensated by new hires could lead in a few years to a strong reduction in the number of family physicians, and to an increasing workload. This tendency is confirmed by other countries [21]. The demographic characteristics of physicians were not significantly different between the different LHUs, as well as the mean number of different antibiotics prescribed per patient in the year, attesting itself around to 2 different antibiotics per patient prescribed

3.2. Strengths and Limitations

The main strength of this study is that by using administrative data we could include all physicians operating in the Lombardy NHS in a large time span. On the other hand, since administrative databases are designed for administrative and reimbursement purposes, some variables are not filled in a database or have a big number of missing values. For example, other GP-related factors, such as education (e.g., specialties, years in practice, or previous working experience) that were found to be associated with prescribing antibiotics [6,10,13,14,16,17] are not available in this database.

High antibiotic consumption is also observed in hospital and emergency settings [2]. However, we could not explore these settings, since the administrative database includes only drugs dispensed by the community pharmacies. Finally, the database does not include indications for the antibiotic prescription, which could be useful to investigate the appropriateness of prescriptions. As pointed out by other international studies, there are many factors involved in the GPs' behaviour in prescribing antibiotics, such as complacency towards patients' desires, fear of possible complications for the patients, and scarce awareness about antibiotic usage [6,7,12]; however, we were not able to investigate such aspects.

3.3. Interpretation within the Context of the Wider Literature

Similarly to us, Huang et al. found a positive association between the age of physicians and the rate of antibiotic prescription [14], while other studies found an inverse or did not find any association between age and GPs' prescribing behaviour [6].

Physicians having a large number of patients with polypharmacy therapy (>200) are prescribed more antibiotics for DDD. Polypharmacy can be seen as a proxy for the clinical complexity of patients who are at higher risk to have bacterial infections. For the same reason in these patients, it may be that GPs use a lower threshold for prescribing antibiotics. A similar result was found in other studies where high practice volume was associated with a higher antibiotics prescription rate [9,11–15]. The same as the other two previous studies [14,15] we did not find any significant difference in prescription behaviour between female and male physicians in terms of DDD prescribed per patient, while in other studies antibiotic prescription was found to be lower among female GPs [7–10]. From 2010 to 2019 the LHUs with the lower number of DDD of antibiotics prescribed per patient were those in the rural areas, where we expect a lower rate of respiratory infections due to air pollution, than in the urban areas. Our results are similar to what was found by Huang et al., where physicians in urban practice were more likely to prescribe antibiotics than their rural colleagues [14].

3.4. Implications for Policy, Practice, and Research

With the aim of facing the increasing threat of antimicrobial resistance, the World Health Organization (WHO), developed 2015 a Global Action Plan on Antimicrobial Resistance, which aims to promote the appropriate use of antibiotics in humans, veterinary and environmental settings [22]. Consistent with the goals of the Global Action Plan, in 2017, the Italian Government, in agreement with the Regions approved the National Plan against antimicrobial resistance (PNCAR) [5]. Among the areas of intervention, the PNCAR includes surveillance of the consumption of antibiotics, with the common goal of reducing the frequency of infections with antibiotic-resistant microorganisms. In our analyses, in the face of a marked reduction in the number of DDD of antibiotics prescribed per patient between 2000 and 2010, in 2018 and 2019 there was a new increment in the number of antibiotics prescribed. These results indicate the need for further educational and surveillance interventions, especially at the level of individual LHUs, to raise GPs' awareness of a more rational use of antibiotics in adult and elderly populations.

4. Methods

4.1. The Italian National Health Service (NHS)

Italian healthcare is provided to all citizens and residents free of charge or against a fee, for the provision of some health services depending on income, age, and disease requirements. The NHS operates through a network of 99 Local Health Units (LHUs) throughout the country [23]. Every Italian resident is registered with a family pediatrician (from 0 up to 13 years old) or a GP (from 14 years and older). Concerning drugs, these are categorized into three classes: class A includes essential drugs provided to citizens free of charge, but, according to regional regulations, a co-payment ticket may be provided for the citizen, class H includes drugs dispensed only in hospital and class C contains drugs not covered by the NHS. All antibiotics belong to class A and are free of charge, with a possible co-payment for the citizen.

4.2. Data Source

Data were extracted from the Administrative Database of the Lombardy Region, Northern Italy, the most populous Italian region, accounting for around 16% of the overall Italian population [24]. The Lombardy region database was described with many details elsewhere [25,26], and it is continuously updated for administrative and reimbursement purposes.

This database includes sociodemographic characteristics of all citizens living in the Lombardy region, and data on prescribed drugs—included in class A—partially or entirely reimbursed by the Italian NHS and dispensed through the community pharmacies. The database contains demographic characteristics of GPs working for the NHS. Each GPs is linked to his/her patients.

All data used in this study were analyzed in compliance with the current laws regarding privacy and data protection.

4.3. Study Population

In the present study, we included GPs younger than 70 years old and with at least 10 patients in charge working in the Lombardy region from 2000 to 2019, who covered 97% of the adult population (40 years or older) residing in the Lombardy region. Because ambulatory specialists (n = 414) and emergency service physicians (n = 21) account for a minimal number of antibiotic prescriptions, the last were excluded from the analysis.

4.4. Data Collection

A number of GP-related factors, previously shown to be associated with variation in antibiotic prescribing were selected from existing literature. These variables were age, sex, LHU of work, adult patients, and older and on polypharmacy patients in charge. Polypharmacy therapy was defined as the exposure to five or more different drugs, excluding antibiotics.

Antibiotics were defined as all substances belonging to the J01 main therapeutic group of the Anatomical Therapeutic Classification (ATC) system. For each GP the mean number of different antibiotics (fifth level of ATC) and the mean number of Defined Daily Doses (DDD) of antibiotics (second level of ATC) prescribed per patient in the index year were calculated. As a proxy of antibiotic prescription appropriateness and/or therapeutic failure prescription, the number of refills of the same antibiotic and of switches among antibiotic classes in a month, done by each GP, were calculated.

Refill was defined as a subsequent filling within 30 days of a previously issued antibiotic prescription. The switch was defined as the replacement of a patient's prescribed antibiotic with another antibiotic (fifth level of ATC).

4.5. Statistical Methods

Characteristics of physicians included in the study were presented as mean and standard deviation, or by median and interquartile range (IQR) as appropriate for continuous variables and frequencies and percentages for categorical variables.

Two multivariable linear regression models were performed to evaluate the association of GPs' characteristics, such as age (categorized as 30–40, 41–50, 51–60, >60 years), sex, Local Health Unit of work, index year, number of patients on polypharmacy in charge (categorized as <100, 100–200, >200), and mean number of antibiotic prescription refills and switches per patient in a month with the mean number of different antibiotics and DDD prescribed per adult patient.

For ordinal predictors (i.e., age groups, calendar years, patients on polypharmacy in charge) dummy variables have been created to compare a category with the previous one, using the coding scheme provided by Walter et al. [27]. Given that physicians included in the analyses could be repeatedly present in the different index years, robust standard errors were calculated [28].

We considered calendar years: 2000, 2010, 2018, and 2019 as in our previous paper [20]. We decided to use also 2018 as the calendar year because, during this year, the European Medicines Agency (EMA) established restrictions on the use of quinolone and fluoroquinolone antibiotics based on increasing scientific evidence, probably influencing the pattern of prescriptions in the following years [29].

Statistical analyses were performed using Stata IC version 15 Software.

5. Conclusions

The knowledge of the GP-related factors that influence their prescribing behaviors towards antibiotics, could allow the policymakers to design targeted educational interventions to prevent unnecessary antibiotic prescription, in order to reduce the worldwide increased risk of antibiotic resistance.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/pharma2020014/s1, Table S1: Geographical distributions of general physicians' (GPs) characteristics from 2000 to 2019.

Author Contributions: Conceptualization, C.F. and I.A.; methodology, I.A. and S.M.; software, S.M.; formal analysis, S.M.; data curation, S.M.; writing—original draft preparation, S.M.; writing—review and editing, C.F., A.N. and I.F. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: In Italy, studies using retrospective aggregated-anonymous data from administrative databases do not require informed consent.

Data Availability Statement: The data used in this study are property of Lombardy region and stored by ARIA S.p.A (Healthcare utilization databases). It is only possible to have access to the data but they cannot be shared. The data access procedure implies the submission of a study protocol to the data owner and the protocol evaluation from a qualified committee. If the research question is of interest for the data owner and the study is well designed, the permission for data access is provided.

Conflicts of Interest: The authors declare no conflict of interest.

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