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ORIGINAL ARTICLE

Primary nonadherence to drugs prescribed by general practitioners: A Dutch database study

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Aim: Primary nonadherence (PNA) is defined as not filling the first prescription for a drug treatment. PNA can lead not only to poor patient outcomes but also to exposure misclassification in written prescription databases. This study aims to estimate PNA in primary care in the Netherlands and to investigate associated factors.

Methods: Patients from the Nivel Primary Care Database (Nivel-PCD) who received a new prescription (>1 year not prescribed) from a general practitioner in 2012 were linked to pharmacy dispensing information of consenting pharmacies based on sex, year of birth, four-digit postal code and at least 50% matching Anatomical Therapeutic Classification codes. PNA was defined as not having a prescription dispensed within 30 days from the prescribing date. PNA was assessed overall and per drug class. The associations between PNA and several patient- and prescription-related characteristics were assessed using mixed-effects logistic regression models.

Results: After matching 86 361 of 396 251 subjects (21.8%) in the Nivel-PCD records to the pharmacy records, this study included 65 877 subjects who received 181 939 new drug prescriptions. Overall, PNA was 11.5%. PNA was lowest for thyroid hormones (5.5%) and highest for proton pump inhibitors (12.8%). Several factors were associated with PNA, such as having comorbidities (odds ratio [OR] 1.46, 95% confidence interval [CI] 1.37-1.56 for >3 active diagnoses, compared to no active diagnoses) or reimbursement status (OR 2.78, 95% CI 2.65-2.92 for not reimbursed drugs compared to fully reimbursed drugs).

Conclusions: A total of 11.5% of newly prescribed drugs were not dispensed. This can lead to overestimation of the actual drug exposure status when using written prescription databases.

KEYWORDS
adherence, statistics and study design, methodology, primary care

1 | INTRODUCTION

Medication nonadherence is the process of patients not using their medication as prescribed. Nonadherence can occur at several stages during medication use, which are commonly classified as the initiation phase (taking the first dose), the implementation phase (taking the right dose at the right regimen) and the discontinuation phase (discontinuing drug use at the right time).[1,2] Nonadherence in each of these phases may lead to poor patient outcomes, such as risk of (re) hospitalization, morbidity and mortality, since patients do not receive the treatment they need.[3–7]

Not only is nonadherence a problem from a medical point of view, but it can also impact pharmacoepidemiologic studies. In studying the relation between drug treatments and health outcomes, routinely collected health data are often used for the assessment of drug exposure, including information on either written or filled prescriptions from primary care. Nonadherence can lead to misclassification of exposure status using these databases, which may in turn lead to biased estimates of the exposure-outcome relationship.[8] Particularly when nonadherence is related to factors that are also associated with the outcome risk, the bias can be unpredictable and may lead to attenuated or exaggerated effect estimates.[9] Insight into the expected level of nonadherence during all phases is therefore important when conducting and interpreting pharmacoepidemiologic research.

Most studies on adherence focus on the implementation and discontinuation phases, whereas the initiation phase is less studied.[10] Nonadherence in the initiation phase is also called primary nonadherence (PNA) and is often measured as the proportion of newly prescribed drugs that are not dispensed at the pharmacy within a certain time window.[11] The main challenge in measuring PNA is that information on prescriptions and dispensings, often from different data sources, must be linked at the patient level for the estimation.[12] A few studies have been able to do so, with one of the first studies being from the UK, in 1993, which assessed PNA within one general practice.[13] Others have used databases with information from more than one practice and assessed PNA for specific drug classes, such as antidepressants, statins and antihypertensives,[14–18] or across all different drug classes, one study from Denmark, one from Canada and three from the United States.[19–23] The reported PNA estimates showed large variation within these studies,[24] which can be partly explained by differences in the methods employed, including the duration of the time window in which PNA is measured.[11] The differences in PNA could also be driven by the drug class and, in relation to that, the beliefs patients may have about the efficacy.[25] For instance, PNA was described as being higher for statins, which are used in the prevention of cardiovascular disease (20.8%), than for drugs that are used for the treatment of depression (10.8%).[24] The population in which PNA is studied could also impact estimates, since PNA has been found to be associated with patient characteristics such as age, sex and socioeconomic status (SES).[19–22,24] Lastly, differences in reimbursement systems may also explain differences in PNA. A meta-analysis revealed that PNA was twice as high in North America compared to Europe (17.0% *vs* 8.5%) due to the presence of universal health coverage in most European countries, but not in the United States.[24] Several other studies have also indicated that costs and reimbursement status are important drivers of PNA.[22,26,27]

Since the underlying health system may play a significant role in PNA, it is important to provide insights into PNA in different countries. We aim to assess PNA in the Netherlands, with its own healthcare and reimbursement system. In this country, all citizens are obliged to have health insurance, which reimburses all care provided by general practitioners (GPs). For almost all other provided care, patients are required to pay a deductible excess of a few hundred euros of the total healthcare costs per year themselves. After this deductible excess is spent, most drugs are fully reimbursed by the health insurance, without copayment, which contrasts with most other European countries.[28] Information about PNA in the Dutch general population is available for a limited number of drugs[15–17] and there is currently no overview of PNA for all drug classes. The aim of this study was thus to provide an overview of PNA in primary care within Dutch general practice and to assess the possible factors associated with PNA.

What is already known about this subject

- Primary nonadherence (PNA), which is not filling the first prescription for a drug treatment, may lead to exposure misclassification in prescription databases.
- Previous studies on PNA showed large variation in estimates, potentially caused by differences in patient characteristics and healthcare systems. Insights into PNA in different countries is therefore needed.

What this study adds

- PNA in the Netherlands was around 10% but varied across drug classes.
- PNA was associated with patient- and prescription-related characteristics, which in part are explained by reimbursement policies.
- Reimbursement policies can impact PNA and hence the potential for exposure misclassification, therefore relevant reimbursement policies should be reported by default in pharmacoepidemiologic studies.

2 | METHODS

This study was designed according to the TEOS framework.[29] The ESPACOMP Medication Adherence Reporting Guideline

(EMERGE) and the guideline for REporting of studies Conducted using Observational Routinely collected health Data, specific to pharmacoepidemiological research (RECORD-PE) were used as guidance in reporting this study.[30,31]

2.1 | Databases and linkage procedure

Data were obtained from the Nivel Primary Care Database (Nivel-PCD),[32] the Foundation for Pharmaceutical Statistics (SFK),[33] Statistics Netherlands[34] and the G-Standaard of the Z-Index.[35] The Nivel-PCD provides a nationally representative database comprising routine data from the electronic medical records of patients from approximately 10% (n = 529) of general practices in the Netherlands. Data include a patient's sex and age, morbidity data coded according to the International Classification of Primary Care (ICPC-1)[36] and information on written prescriptions, including date of prescription and the Anatomical Therapeutic Classification (ATC) code.[37] The SFK databases contain information on pharmacy dispensings, including ATC code, dispensing date and reimbursement status (yes or no). Neighborhood SES was obtained from Statistics Netherlands, and drug pricing information and maximum reimbursed price per drug were obtained from the G-Standaard.

Subjects enrolled in a general practice in the Nivel-PCD records from 1 January 2011 to 31 December 2013 were linked to individual data from one of the nearby participating SFK pharmacies that consented to linkage (n = 186). To ensure matching, the sex, year of birth and four-digit postal code from the Nivel-PCD records had to fully match the SFK data, and at least 50% of the ATC codes of all drugs prescribed by GPs had to match per patient within a lag period of 6 days. After matching, each patient was assigned a unique patient identifier indicating the match in the Nivel-PCD and SFK data. Neighborhood SES was linked with the patient's four-digit-postal code and pricing information was linked with ATC code. For this study, we reused the most recently linked Nivel-PCD and SFK datasets, with data linked for patients registered at NIVEL-PCD from 2011 to 2013.

2.2 | Study population

All successfully matched subjects who received a prescription for a new drug in 2012 – defined as not being prescribed in the prior 365 days – were included in the study population. Patients could receive a new written prescription for multiple drugs. All prescriptions with invalid ATC codes (e.g., "Y" or "Z") were excluded for the analysis, as well as prescriptions that are not dispensed via the outpatient pharmacy in the Netherlands, such as influenza vaccines or expensive drugs (Supporting Information Table S1). To ensure the inclusion of newly prescribed drugs only, all prescriptions with a record of dispensing before the first record of a written prescription were excluded.

2.3 | Definition of PNA

PNA was assessed for all newly written prescriptions prescribed in 2012. For this assessment, the SFK database was searched for a record of dispensing from a pharmacy within 30 days of the prescription date, matched on ATC code (fifth level). PNA was defined as not having a prescription dispensed within 30 days from the prescribing date.

2.4 | Assessment of associated factors

On the patient level, we assessed the following characteristics: sex, age (categorized as 0-20 years, 21-40 years, 41-60 years, 61-80 years, and 80 years and older), neighborhood SES (the highest and lowest quintiles were categorized as high and low SES scores, respectively, while the middle three quintiles were categorized as a medium SES score), the number of active diagnoses on the first day of the prescription month (categorized as 0, 1-3 and >3), the number of GP contact moments in the 12 months preceding the prescription month (categorized as 0, 1-5 and >5), the number of different drugs dispensed in the 3 months preceding the prescription month (defined on the fourth ATC level, categorized as 0, 1-5 and >5) and the presence of specific comorbidities (cardiovascular diseases, diabetes mellitus, respiratory diseases, psychological disorders and malignancies; for ICPC codes, see Supporting Information Table S2).

On the prescription level, we assessed the quarter of the year in which the prescription date fell and the reimbursement status. Reimbursement status was categorized as follows: fully reimbursed, partially reimbursed (if the costs are higher than the maximum reimbursed price), conditionally reimbursed (only reimbursed after drug use for more than 6 months; Supporting Information Table S3)[38] or not reimbursed (e.g., vitamins or acetaminophen). The reimbursement status could change every month, thus information about reimbursement status was updated on the first day of every month.

2.5 | Data analysis

Baseline characteristics of the included subjects were assessed on 1 January 2012 and described as proportions.

PNA was calculated as the proportion of the total number of newly written prescriptions that were not dispensed within 30 days of the prescription date. PNA was assessed overall and per ATC class (first level). In addition, PNA was assessed for drug classes that are frequently prescribed in primary care in the Netherlands (Table 1).[39]

The association between PNA and the patient- and prescription-related characteristics was assessed using mixed-effects logistic regression, with a random intercept per subject, per general practice and per pharmacy. The following characteristics were assessed: age, sex, neighborhood SES, the number of active diagnoses, the number

TABLE 1 Anatomical Therapeutic Classification (ATC) codes of frequently prescribed drug (classes)

Drug class	ATC code(s)
Proton pump inhibitors	A02BC
Laxatives	A06
Insulins	A10A
Oral antidiabetics	A10B
Acetylisalicylic acid	B01AC06
Antihypertensives	C02, C03, C07, C08, C09
Statins	C10AA
Dermal steroids	D07
Hormonal contraceptives	G03A
Thyroid hormones	H03A
Systemic antibiotics	J01
Nonsteroidal anti-inflammatory drugs	M01A
Benzodiazepines	N05AB, N05CD
Selective serotonin inhibitors	N06AB
Inhalation drugs for asthma/COPD	R03A, R03B
Antihistaminics for systemic use	R06

of GP contact moments in the preceding 12 months, the number of different drugs dispensed in the preceding 3 months, the quartile in which the prescription fell and the reimbursement status. All fixed effects were estimated both separately in a univariable analysis and combined in a multivariable analysis. Multicollinearity was checked and variables were removed if necessary. The level of significance was set at 0.05.

As sensitivity analyses, we assessed PNA by applying a definition of dispensing within 90 days and 365 days of the prescription date and by matching prescription data and dispensing data at the fourth ATC level.

Data analysis was performed using the statistical software package R.[40]

3 | RESULTS

The Nivel-PCD records included 396 251 subjects with at least one written prescription during 2011-2013. Of those, 244 820 (61.8%) could be potentially matched to patients of consenting pharmacies in the SFK database based on sex, year of birth and four-digit postal code. After matching on ATC codes, 86 361 subjects (35.3%) were matched (Figure 1). The characteristics of matched and unmatched subjects are presented in Supporting Information Table S4. Of the 86 361 matched subjects, 65 877 subjects initiated one or more new drug treatments in 2012 from 119 different GP practices, which were dispensed by 126 different pharmacies. In total, 181 939 new prescriptions were prescribed in 2012. The median number of new prescriptions per subject prescribed during 2012 was two (range one to four).

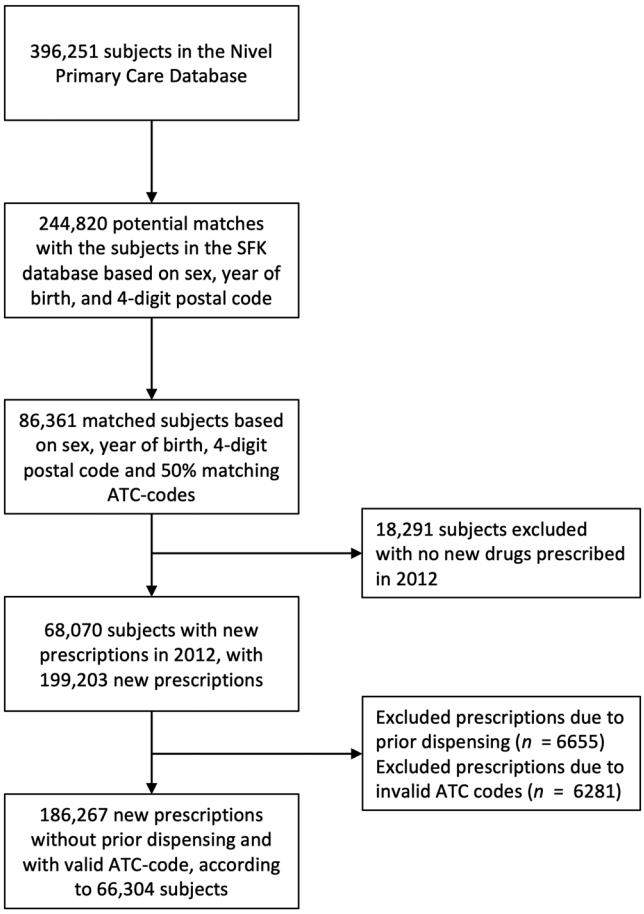

FIGURE 1 Flowchart of the inclusion of subjects in the final dataset

The baseline characteristics of the included 65 877 subjects are presented in Table 2. Most patients were aged 41-60 years (33.3%) and 59.1% were women. Approximately half of the study population was classified as living in a neighborhood with a medium SES, 20% in a neighborhood with a low SES and 30% in a neighborhood with a high SES. The majority had at least one active diagnosis on 1 January 2012 (77.7%), at least one contact moment with the GP in 2011 (89.4%) and one or more drugs dispensed in the last quartile of 2011 (66.9%). Comorbidities that were most present were respiratory diseases (13.5%) and cardiovascular diseases (10.3%).

3.1 | PNA overall and per drug class

The overall PNA was 11.5% (20 970/181393), defined as newly prescribed drugs that were not dispensed at the pharmacy within 30 days of the prescription date. PNA varied among ATC classes (Table 3), with lower PNA for drugs prescribed to treat cardiovascular disease (ATC Class C, 8.3%) and genito-urinary system drugs and sex hormones (ATC Class G, 8.5%). In contrast, PNA was highest for antineoplastic and immunomodulating drugs (ATC Class L, 19.5%) and

TABLE 2 Baseline characteristics of the 65 877 included subjects, assessed at 1 January 2012

	Number of subjects (%)	Number of new prescriptions (%)
Sex		
Male	26 974 (40.9)	68 999 (37.9)
Female	38 903 (59.1)	112 940 (62.1)
Age		
0-20 years	9782 (14.8)	20 754 (11.4)
21-40 years	12 065 (18.3)	32 032 (17.6)
41-60 years	21 964 (33.3)	60 548 (33.3)
61-80 years	19 067 (28.9)	58 278 (32.0)
80+ years	2999 (4.6)	10 327 (5.7)
Neighborhood socioeconomic status[a]		
Low	13 529 (20.5)	37 331 (20.5)
Medium	32 705 (49.6)	90 593 (49.8)
High	19 494 (29.6)	53 505 (29.4)
Missing	149 (0.2)	510 (0.3)
Number of active diagnoses on 1 January 2012		
0	14 663 (22.3)	32 089 (17.6)
1-3	37 662 (57.2)	100 641 (55.3)
>3	13 552 (20.6)	49 209 (27.0)
Number of GP contact moments in 2011		
0	6964 (10.6)	14 805 (8.1)
1-5	36 206 (55)	90 207 (49.6)
>5	22 707 (34.5)	76 927 (42.3)
Number of different drugs dispensed last quartile of 2011[b]		
0	21 835 (33.1)	51 251 (28.2)
1-5	36 183 (54.9)	100 407 (55.2)
>5	7859 (11.9)	30 281 (16.6)
Comorbidities		
Cardiovascular disease	6764 (10.3)	22 504 (12.4)
Diabetes mellitus	6052 (9.2)	19 941 (11.0)
Respiratory diseases	8877 (13.5)	29 757 (16.4)
Psychiatric diseases	4453 (6.8)	14 702 (8.1)
Malignancy (excluding skin malignancy)	3325 (5.0)	11 357 (6.2)

[a]Neighborhood socioeconomic status (SES) was divided by quintile (the highest and lowest quintiles were categorized as high and low SES scores, respectively; the middle three quintiles were categorized as a medium SES score). Quintiles were based on the total Nivel-PCD population and not on the matched population.
[b]Defined on the fourth ATC level.

drugs for blood and blood-forming organs (ATC Class B, 16.1%). Within drug classes that are frequently used in primary care, PNA was 9.9%. Furthermore, PNA was highest for proton pump inhibitors (PPIs) and nonsteroidal anti-inflammatory drugs (NSAIDs) (12.8% and 11.8%, respectively) and lowest for thyroid hormones and oral antidiabetics (5.5% and 5.6%, respectively) (Table 3).

TABLE 3 Primary nonadherence[a] according to different drug classes

Drug class Anatomical chemical therapeutic class (first level)	Not dispensed/ prescribed	Proportion primary nonadherence (95% CI)
Alimentary tract and metabolism (A)	3262/23360	14.0 (13.5-14.4)
Blood and blood forming organs (B)	790/4992	15.8 (14.8-16.8)
Cardiovascular system (C)	1180/14262	8.3 (7.8-8.7)
Dermatologicals (D)	2674/24888	10.7 (10.4-11.1)
Genito-urinary system and sex hormones (G)	762/8948	8.5 (7.9-9.1)
Systemic hormonal preparations, excluding sex hormones and insulins (H)	498/4243	11.7 (10.8-12.7)
Anti-infective for systemic use (J)	3170/28295	11.2 (10.8-11.6)
Antineoplastic and immunomodulating agents (L)	134/730	18.4 (15.5-21.2)
Musculo-skeletal system (M)	1828/15213	12 (11.5-12.5)
Nervous system (N)	2524/19202	13.1 (12.7-13.6)
Antiparasitic products, insecticides and repellents (P)	161/1578	10.2 (8.7-11.7)
Respiratory system (R)	2232/23149	9.6 (9.3-10.0)
Sensory organs (S)	1740/13011	13.4 (12.8-14.0)
Various (V)	15/68	22.1 (12.2-31.9)
Specific drug classes		
Proton pump inhibitors	890/6965	12.8 (12.0-13.6)
Laxatives	820/7110	11.5 (10.8-12.3)
Insulins	45/461	9.8 (7.1-12.5)
Oral antidiabetics	60/1079	5.6 (4.2-6.9)
Acetylsalicylic acid	78/715	10.9 (8.6-13.2)
Antihypertensives	593/8593	6.9 (6.4-7.4)
Statins	194/2686	7.2 (6.2-8.2)
Dermal steroids	986/13032	7.6 (7.1-8.0)
Hormonal contraceptives	233/2835	8.2 (7.2-9.2)
Thyroid hormones	18/325	5.5 (3.1-8.0)
Systemic antibiotics	2736/24640	11.1 (10.7-11.5)
Nonsteroidal anti-inflammatory drugs	1625/13727	11.8 (11.3-12.4)
Benzodiazepines	113/1705	6.6 (5.4-7.8)
Selective serotonin inhibitors	52/829	6.3 (4.6-7.9)
Inhalation drugs for asthma/ chronic obstructive pulmonary disease (COPD)	544/6554	8.3 (7.6-9.0)
Antihistaminics for systemic use	540/5159	10.5 (9.6-11.3)

[a]Primary nonadherence was defined as not having a prescription dispensed within 30 days from prescription date.

TABLE 4 Results of the mixed-effects logistic regression model[a] assessing the association between patient and prescription characteristics and primary nonadherence[b]

	% Primary nonadherence (not dispensed/prescribed)	Univariate analysis OR (95% CI)	Multivariable analysis OR (95% CI)
Sex			
Male	11.7 (8092/68999)	Ref	Ref
Female	11.4 (12 878/112940)	0.95 (0.92-0.99)	0.96 (0.92-0.99)
Age			
0-20 years	11.3 (2345/20754)	1.13 (1.07-1.20)	1.13 (1.06-1.20)
21-40 years	12.1 (3889/32032)	1.15 (1.09-1.21)	1.19 (1.12-1.25)
41-60 years	11.0 (6634/60548)	Ref	Ref
61-80 years	11.8 (6870/58278)	1.08 (1.03-1.13)	1.04 (0.99-1.09)
80+ years	11.9 (1232/10327)	1.11 (1.02-1.21)	1.05 (0.96-1.14)
Socioeconomic status[c]			
Low	10.9 (4143/37841)	Ref	Ref
Medium	10.9 (9944/91103)	0.92 (0.86-0.98)	0.93 (0.86-0.99)
High	12.4 (6679/54015)	0.90 (0.83-0.98)	0.92 (0.85-0.99)
Number of active diagnoses on the first day of the prescription month			
0	9.8 (2689/27352)	Ref	Ref
1-3	11.4 (11 223/98512)	1.10 (1.05-1.16)	1.24 (1.17-1.31)
>3	12.6 (7058/56075)	1.18 (1.12-1.25)	1.46 (1.37-1.56)
Number of GP contact moments in the year before the prescription month			
0	9.3 (1187/12742)	Ref	NA[f]
1-5	11.0 (9534/86372)	1.23 (1.15-1.31)	NA
>5	12.4 (10 249/82825)	1.39 (1.29-1.49)	NA
Number of different drugs dispensed in the 90 days before the prescription month[d]			
0	13.5 (6128/45523)	Ref	Ref
1-5	11.4 (3815/33349)	0.87 (0.84-0.91)	0.85 (0.82-0.89)
>5	10.7 (2658/24880)	0.87 (0.82-0.92)	0.80 (0.75-0.85)
Prescription date			
Q1-2012	13.2 (6677/50505)	Ref	Ref
Q2-2012	12.3 (5792/47032)	0.90 (0.86-0.93)	0.90 (0.86-0.93)
Q3-2012	10.2 (4181/41101)	0.69 (0.66-0.72)	0.68 (0.65-0.71)
Q4-2012	10.0 (4320/43301)	0.67 (0.64-0.70)	0.68 (0.65-0.71)
Reimbursement status[e]			
Fully reimbursed	10.6 (15 244/143607)	Ref	Ref
Not reimbursed	21.7 (3081/14171)	2.73 (2.60-2.86)	2.78 (2.65-2.92)
Partially reimbursed	9.1 (677/7413)	0.87 (0.80-0.94)	0.88 (0.81-0.96)
Conditionally reimbursed	11.8 (1968/16748)	1.08 (1.02-1.14)	1.09 (1.04-1.15)

[a]Mixed-effects logistic regression, with patient, general practice and pharmacy as random effects.
[b]Primary nonadherence was defined as not having a prescription dispensed within 30 days from prescription date.
[c]Neighborhood socioeconomic status (SES) was divided by quintile (the highest and lowest quintiles were categorized as high and low SES scores, respectively; the middle three quintiles were categorized as a medium SES score).
[d]Defined on the fourth ATC level.
[e]Drugs were categorized as partially reimbursed if the costs were higher than the maximum reimbursed price. Drugs were categorized as conditionally reimbursed if they were only reimbursed after use for more than 6 months.
[f]Excluded from the multivariate analysis due to multicollinearity with the number of active diagnoses.

3.2 | Patient-related factors associated with PNA

Different patient characteristics were associated with PNA in both the univariable and multivariable analyses (Table 4). On the patient level, females were less likely to be primary nonadherent than males (odds ratio [OR] 0.96, 95% confidence interval [CI] 0.92-0.99). Moreover, patients aged 0-20 years and 21-40 years were more likely to be primary nonadherent than patients aged 41-60 years (OR 1.13, 95% CI 1.06-1.20 and OR 1.19, 95% CI 1.12-1.25, respectively). Patients living in a neighborhood with a high or medium SES were less likely to be primary nonadherent (OR 0.93, 95% CI 0.86-0.99 and OR 0.92, 95% CI 0.85-0.99, respectively) compared to those in low SES neighborhoods. In addition, having more different diagnoses or GP contact moments increased the likelihood of displaying PNA. Due to collinearity between these two factors, only the number of active diagnoses was included in the multivariate model, resulting in ORs of 1.24 (95% CI 1.17-1.31) and 1.46 (95% CI 1.37-1.56) for one to three active diagnosis and more than three active diagnoses, respectively, compared to subjects with no active diagnoses. Prevalent drug users were less likely to be primary nonadherent. The OR for PNA for patients having one to five drugs dispensed in the preceding 90 days was 0.85 (95% CI 0.82-0.89) compared to naïve drug users, and 0.80 (95% CI 0.75-0.85) for patients who had more than five drugs dispensed.

3.3 | Prescription-related factors associated with PNA

On the prescription level, drugs with partial reimbursement were less likely to not be dispensed compared to fully reimbursed drugs (OR 0.88, 95% CI 0.81-0.96), whereas drugs that were not reimbursed and those that were reimbursed conditionally were more likely to not be dispensed (OR 2.78, 95% CI 2.65-2.92 and OR 1.09, 95% CI 1.04-1.15, respectively). Patients receiving prescriptions that should be filled during the first quarter of 2012 were more likely to exhibit PNA when compared to those receiving prescriptions in the other quarters, with PNA being least likely for patients receiving prescriptions that should be filled during the last quarter of 2012 (OR 0.68, 95% CI 0.65-0.71, compared to the first quarter). This decreasing PNA over time was observed for both fully reimbursed drugs (12.3-8.9%) and partially reimbursed drugs (12.5-6.7%), but to a lesser extent for drugs that were only reimbursed after use for more than 6 months (12.7-11.4%) or drugs that were not reimbursed (23.5-21.4%).

3.4 | Sensitivity analyses

The sensitivity analyses using different durations of time for defining PNA showed similar results to when 30 days were applied, namely 10.9% and 9.4% PNA for 90 and 365 days, respectively, compared to 11.5%. The sensitivity analysis assessing PNA at the fourth ATC level resulted in a PNA estimate of 11.2%, similar to the estimate at the fifth ATC level.

4 | DISCUSSION AND CONCLUSION

Overall, 11.5% of all newly prescribed drugs that were included in this study did not have a record of dispensing in the pharmacy database within 30 days of the prescription date. However, this percentage differed across different drug classes. Several patient and prescription characteristics were associated with PNA, such as age, neighborhood SES, the presence of comorbidities and polypharmacy, the reimbursement status, the date of prescription and drug class.

The estimate of PNA is in line with results from other European studies, which all obtained PNA estimates around 9%. Moreover, the differences in PNA between drug classes were similar to patterns found in Denmark, such as relatively high levels of PNA for PPIs, salicylic acid and NSAIDs compared to a lower level of PNA for antidepressants, antihypertensives and antidiabetic agents.[19] PNA could thus to some extent be explained by the indication for the drug as medicines prescribed for chronic (symptomatic) diseases could be considered as having a higher use need when compared with medicines that can be used as needed (NSAIDs) and as such patients are more likely to get these dispensed. In addition, patients' perceived need for a drug can impact PNA.[41] The association between SES and PNA was also in line with what others have assessed, with a lower SES being related to a higher level of nonadherence.[19] The relation between age and PNA, however, varied between previous studies. We found a U-shaped association, which was also found by Shin et al, in drugs used for chronic conditions, but not for drugs used for acute conditions. Other studies have also shown an effect of age, but these results are all inconsistent: the level of PNA either increased with age[21,22] or decreased.[19,23,42] These conflicting results of the effect of age may be caused by differences in how healthcare is organized or by different reimbursement rules between different age groups. Also, with regard to sex, the results were conflicting. Most studies found no significant association,[19,22,23] while Shin et al found that women were more adherent to acute treatments and men to chronic treatments.[20] Probably, the effect of sex is only minor, if it indeed exists.

The negative relation between the number of drugs in use and the likelihood of a patient being primary nonadherent was also observed in Canada. In Denmark, however, an inverse relation was observed.[19,23] In the Netherlands, this negative relation might be explained by the reimbursement system, where patients are required to pay a deductible excess of a few hundred euros of the total healthcare costs per year themselves (€220 in 2012). After this deductible excess is spent, most drugs are fully reimbursed by health insurance, without copayment. The more drugs are in use, the higher the chance that the deductible excess is used and new drugs are reimbursed, resulting in lower levels of PNA. Since the deductible excess is reset to zero at the beginning of each year,[43] this system may also explain the association between prescription date and PNA. This deductible is not specific to the Dutch situation, but is also in place in Denmark, Finland, Iceland, Ireland, Norway, Sweden and Switzerland.[28] Also for these countries, the level of adherence may thus vary through the year due to national reimbursement systems.

The strong association between drugs without reimbursement and PNA was also noted in studies in Canada and the United States.[22,23] In addition, we found an association between drugs being conditionally reimbursed and the level of PNA. In the Netherlands there are specific conditions attached to the reimbursement of specific drug classes, such as for PPIs, H2-receptor antagonists, laxatives and antihistamines used for allergies, which are only reimbursed for chronic use, defined as being used for 6 months or longer. This implies that when these drugs are prescribed for the first time, they are not reimbursed. PPIs and H2-receptor antagonists were added on 1 January 2012 to this list of conditionally reimbursed drugs.[38] It was found that the proportion of NSAID users who filled a prescription for a PPI decreased in 2012 compared to 2011 (69.0% *vs* 73.3%), while the number of prescriptions issued by GPs remained the same in these years, despite an initial decrease after changes in reimbursement policy.[43,44] Reimbursement rules thus have an impact on the proportion of subjects that fill their prescription at the pharmacy.

In contrast, drugs that were partially reimbursed showed a lower level of PNA. However, the copayment for these drugs was generally low (e.g., €1.50 per month for digoxin). Moreover, the treating physician may have a reason to initiate specifically the drug with the copayment among other options without copayment, which may explain why PNA is lower for these drugs.

The fact that these prescription-related factors associated with PNA could largely be explained by specific Dutch reimbursement rules regarding patient (co)payment highlights the need for transparent reporting on the health system and reimbursement rules that are in place. Although in Europe we expect many countries to have similar reimbursement systems, requiring copayment, it is important to reflect on the possible impact of these for the data used. In this way, those interpreting results from pharmacoepidemiological studies can also make an estimate of the expected level of adherence to a particular drug.

4.1 | Strengths and limitations

A strength of this study was the fact that written prescription data and dispensing data could be linked for a large representative sample from the general population. Furthermore, we provided an overview of PNA for all medication instead of a select set of drug classes.

One of the limitations of this study was the fact that the matching procedure was based, among other things, on a minimum of 50% matching ATC codes in the Nivel-PCD data and the SFK database. Subjects with a higher degree of nonadherence were more likely to be excluded, which may have led to an underestimation of PNA. Especially, subjects receiving one to three (incident or prevalent) prescriptions were often not linked to subjects in the SFK database: 4.4% of all subjects who received one to three prescriptions during 2011-2013 could be linked, compared to 27.2% of all subjects who received four or more prescriptions (Table S4). In the group that received one to three prescriptions, nonadherence to only one or two newly prescribed prescriptions would have led to exclusion of the study population, instead of measuring this as PNA. However, these subjects were also responsible for fewer new prescriptions (0.75 newly prescribed drugs per subject) than the group that had more drugs in use (2.11 newly prescribed drugs per subject), thereby probably limiting the impact on the estimation of PNA. Nevertheless, the matching procedure could also have led to biased estimates of the association between the number of drugs in use and the number of comorbidities and PNA, since those subjects also probably had more comorbidities.

Furthermore, the presence of a dispensing record does not automatically mean that the drug is taken by the patient. For example, for statins, antidepressant agents and antihypertensive agents, it has been shown that approximately 20-30% of all new users fill only one prescription, of which a proportion do not initiate at all.[45–47] Moreover, patients do not always collect the drugs that have been dispensed for them. Information on whether or not drugs are being collected was not available in the SFK data and can also lead to an underestimation of PNA.

PNA could also be overestimated for drugs that may be obtained without being recorded in the outpatient pharmacy database. This may be the case for drug prescriptions that can also be obtained over the counter, such as NSAIDs, PPIs and antihistamines. Obtaining these drugs as pharmacy purchases may in some cases be less expensive than obtaining the drug as pharmacy dispensing. The level of PNA, however, did not show large differences between drugs that can be obtained over the counter (3875/32961, 11.7%) and those that cannot be obtained over the counter (17 095/148432, 11.5%).

Another possible explanation for PNA is the existence of "delayed prescriptions" for antibiotics. These prescriptions do not necessarily have to be collected at the pharmacy, but only when the complaints do not resolve within a certain time window, which may explain the relatively high level of PNA for systemic antibiotics (11.1%). Using a written prescription database, however, would lead to overestimation of the true exposure to antibiotics.

PNA can also be overestimated for drugs that are dispensed in the in-hospital outpatient pharmacy, such as antineoplastic medicines. The antineoplastic medicines accounted for only 0.4% of all prescriptions and we do not expect that other drugs are frequently dispensed in the in-hospital outpatient pharmacy, limiting the impact on the overall estimate of PNA. Yet, PNA estimates should be interpreted with caution for these types of drugs. Patients visiting multiple pharmacies may be another reason that dispensations may not be recorded. However, most patients (>80%) receive all their medicines from a single pharmacy,[48] and the matching procedure based on ATC codes also limits the impact of patients visiting multiple pharmacies. In addition, patients can collect their prescription after more than 30 days, although sensitivity analyses with longer windows indicate that this share was limited (10.4% for 90 days instead of 11.5%). Prescription errors can further explain a proportion of PNA. However, we do not expect this to be common for the

frequently prescribed drug classes, and sensitivity analysis with fourth ATC level matching did not lead to significantly different estimates (11.2% instead of 11.5%).

Another limitation was the fact that we used data from 2012. Nevertheless, we expect no major differences to the current situation. The associations between patient characteristics and PNA are assumed to remain the same, and there were also no major changes in the reimbursement system, except for the increase in the deductible excess (€385 in 2021, compared to €220 in 2012).

4.2 | Implications

Although the level of PNA differed among drug classes, the amount of PNA was around 10% for most frequently prescribed drug classes. This means that roughly 10% of all drug treatments are not initiated, which has both clinical and methodological implications. For clinical practice, the implication is that nonadherent patients are not being treated as intended by their physician, potentially leading to poor patient outcomes, increased health expenditure and hence increased costs.[3–7,49,50] From a methodological point of view, the implication is that, due to PNA, exposure status estimations based on written prescription data (e.g., CPRD[51] or BIFAP[52]) may suffer more from exposure misclassification than exposure status estimations based on filled prescription data (e.g., the PHARMO database Network[53] or Medicaid).[54] This may potentially lead to biased estimates of the association between drug treatments and health outcomes.[8,13] Since PNA is found to be associated with patient characteristics that may also be associated with the outcomes being studied, the misclassification can be differential, potentially resulting in unpredictable bias of the effect estimate.[9] Yet the impact of 10% exposure misclassification due to nonadherence and the difference in the level of PNA between subgroups are likely limited. For example, a simulation study of the impact of exposure misclassification on effect estimates revealed that a 10% nondifferential nonadherence could cause an approximate 10% bias toward the null effect, and the impact of differential misclassification was also limited.[55]

4.3 | Conclusions

To conclude, one out of nine prescriptions initiated by a GP is not dispensed from a pharmacy. PNA varies across drug classes, ranging between 5.5% for thyroid hormones and 12.8% for PPIs. PNA was found to be associated with several patient- and prescription-related characteristics, which could to some extent be explained by reimbursement levels. Therefore, in line with item 19.1.a in the RECORD-PE guideline for reporting on pharmacoepidemiological studies,[30] we recommend that researchers elaborate on the health and reimbursement system and the potential for exposure misclassification due to PNA. Moreover, when researchers utilize prescribing data, we recommend that they provide estimates of (a) the amount of PNA for the specific drugs under investigation and (b) the possible impact that PNA might have on effect estimates. In addition, for drugs with high levels of PNA, GP databases are less suitable, and claims or dispensing databases should be chosen instead.

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COMPETING INTEREST

No authors report any conflict of interest.

CONTRIBUTORS

M.H. was involved in the conception and design of the study, statistical analysis and interpretation of data, drafting and critical revision of the manuscript. S.R. was involved in statistical analysis and interpretation of data. R.G. was involved in conception and design of the study and critical revision of the manuscript. K.H. was involved in acquisition of data, interpretation of data and critical revision of the manuscript. A.B. was involved in conception and design of the study, interpretation of data and critical revision of the manuscript. O.K. was involved in conception and design of the study, interpretation of data and critical revision of the manuscript. H.G. was involved in conception and design of the study, interpretation of data and critical revision of the manuscript.

DATA AVAILABILITY STATEMENT

Data subject to third-party restrictions. The data that support the findings of this study are available from Nivel. Restrictions apply to the availability of these data, which were used under license for this study.

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