

# Validation of low-dose aspirin prescription data in The Health Improvement Network: how much misclassification due to over-the-counter use?

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## ABSTRACT

**Purpose** We aimed to quantify the extent of over-the-counter (OTC) low-dose aspirin use among patients in The Health Improvement Network (THIN) in the UK.

**Methods** In September 2013, a random sample of low-dose aspirin users (75 past users and 75 never users) was identified based on prescriptions recorded in THIN. Primary care practitioners (PCPs) were sent questionnaires to provide information on patients' use of OTC low-dose aspirin.

**Results** One hundred and forty valid questionnaires were received (93.30% [95%CI: 88.16–96.34] response rate). Current use of low-dose aspirin was reported by PCPs in 4.23% (95%CI: 1.45–11.70) ( $n=3$ ) of past users (OTC use in one patient) and in 2.9% (95%CI: 0.78–9.70) ( $n=2$ ) of never users (OTC use in one patient). In addition, PCPs reported past use of low-dose aspirin in 88.70% (95%CI: 79.31–94.18) ( $n=63$ ) of past users (all prescribed; none as OTC) and in 2.82% (95%CI: 0.78–9.70) ( $n=2$ ) of never users (as OTC). Among past users, PCPs reported the indication for low-dose aspirin as primary cardiovascular disease (CVD) prevention in 63.16% (95%CI: 50.18–74.48) of patients and secondary CVD prevention in 31.58% (95%CI: 21.00–44.48) of patients. Corresponding percentages based on THIN were 78.95% (95%CI: 66.71–87.53) and 21.1% (95%CI: 12.47–33.29), respectively.

**Conclusion** Our findings show the small impact of potential misclassification of low-dose aspirin use in THIN due to unrecorded OTC use. The small proportion of false negatives confirms the utility of THIN for utilization and outcome studies of low-dose aspirin. © 2015 The Authors. *Pharmacoepidemiology and Drug Safety* published by John Wiley & Sons Ltd.

KEY WORDS—low-dose aspirin; nonprescription drugs; over-the-counter drugs; pharmacoepidemiology

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## INTRODUCTION

Low-dose aspirin (acetylsalicylic acid; 75–150 mg/day) has been extensively studied using large electronic healthcare databases.<sup>1–12</sup> These databases generally contain information on prescribed and/or dispensed medication but do not necessarily capture data on medications obtained over-the-counter (OTC). Epidemiological studies assessing drug utilization are reliant on accurate exposure data for a true description of use, while for studies evaluating the safety or effectiveness of medicines, it is important that both accurate exposure and clinical outcome data are obtained in order to calculate valid estimates of effect. Thus, when using electronic

healthcare databases to assess a medication that is available both via prescription and OTC, it is imperative that data on OTC use are considered. In the United Kingdom (UK), low-dose aspirin is available as OTC medication, hence the potential for exposure misclassification when studying use of the drug in the UK via electronic healthcare databases. The Health Improvement Network (THIN) primary care database has been the data source for a large number of studies concerning use of low-dose aspirin in the UK. We carried out a validation study that aimed to quantify the extent of low-dose aspirin use obtained OTC by patients in THIN.

## METHODS

### Data source

The Health Improvement Network is a population-based computerized medical research database that

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contains anonymized patient data systematically recorded by primary care practitioners (PCP's) in the UK.<sup>13</sup> The database holds over 80 million patient years of computerized prospectively collected data and covers approximately 6% of the UK population.<sup>14</sup> Participating PCPs record data as part of routine patient care and supply this information to THIN for anonymization and organization for use in research projects. The computerized information includes demographics, details from PCPs visits, diagnoses from specialists' referrals and hospital admissions, results of laboratory tests, and a free-text section. Prescriptions issued by the PCP are generated directly from the computer. The Read classification<sup>15</sup> is used to code specific diagnoses, and a drug dictionary based on data from the GEMSCRIPT classification is used to code drugs.<sup>16</sup> The database is representative of the UK population with regard to age, sex, and geographic distribution;<sup>17</sup> more than 380 research articles have been published using data from this source.<sup>14</sup>

#### *Study population and identification of low-dose aspirin users*

Individuals in THIN aged 40–84 years between January 2000 and December 2009 were eligible to enter the study population upon meeting the inclusion criterion of having at least one contact with their PCP, not including the issue of prescriptions, over a period of 2 years. Members of the study population were also required to have a history of at least 3 years' computerized prescriptions and have no prior record of low-dose aspirin use or cancer. The date an individual met all these criteria was considered her or his study entry date. From this date, we identified all new users of low-dose aspirin, as well as individuals never exposed to low-dose aspirin at the time of the most recent available version of the database (September 2013). We then identified discontinuers of low-dose aspirin as patients whose last prescription was issued more than 1 year prior to September 2013 (past users) as well as patients never exposed to low-dose aspirin (never users). Only past users and never users belonging to practices collaborating with THIN, by means of agreeing to provide information via questionnaires when requested, were retained in the study population.

#### *Study sample*

We selected a random sample of 75 patients in each low-dose aspirin exposure group (past users and never users;  $n=150$ ). Each sample had an equal number of individuals ( $n=15$ ) in the following age strata: 40–49,

50–59, 60–69, and 80–89 years. For the 75 patients in the past user group, the indication for their previous aspirin use was ascertained from THIN and classified as either primary or secondary cardiovascular disease (CVD) prevention. To identify patients whose indication had been secondary CVD prevention, a computerized algorithm was used that searched their electronic medical records in THIN for Read codes suggestive of CVD. Read codes recorded any time before the first low-dose aspirin prescription and up to 30 days after were included, and the information closest to the date of the first low-dose aspirin prescription was prioritized. These patients were then classified into the following indication categories: myocardial infarction (MI), unstable angina, revascularization, cerebrovascular disease, peripheral artery disease, and ischaemic heart disease (IHD) unspecified. In addition, patients with MI, unstable angina, and IHD comprised a category, "coronary diseases." All remaining past users who did not have a relevant Read code to suggest that the indication was secondary CVD prevention were assumed to have received low-dose aspirin for primary CVD prevention. Information on gender, lifestyle characteristics (smoking and body mass index), and comorbidities (diabetes, hypertension, and hypercholesterolemia) was extracted from the database for all patients in the two aspirin study groups any time before the latest date available in the database, prioritizing the closest recorded entry to that date.

#### *Questionnaire sent to PCPs*

Between January and March 2014, PCPs for the 150 patients in our study sample received a postal questionnaire containing mostly closed-ended questions about their patients' use of low-dose aspirin at the time the PCP filled the questionnaire (January to March 2014). If a patient was reported by the PCP to be currently using aspirin, the PCP was asked to provide information about whether this was prescribed or obtained OTC, the length of time the patient had taken it, and the indication. For patients reported to be not currently taking low-dose aspirin, the PCP was asked to provide information regarding whether they had ever used low-dose aspirin previously and whether this previous use was prescribed or obtained OTC, the length of time they had taken the medication, the indication, and the reason for discontinuation. In addition, information about current use or use in the last 3 months of OTC non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), and histamine-2 receptor antagonists ( $H_2$ RAs) was

requested. The questionnaire sent to the PCPs to complete is shown in the Supporting Information.

### Analysis

The proportion of individuals in both low-dose aspirin exposure groups (past users and never users) reported by the PCP to be currently or have previously used low-dose aspirin was calculated. Baseline characteristics of patients in the two study groups (past users and never users) and indications for low-dose aspirin were evaluated. Among past users, we ascertained the reasons for low-dose aspirin discontinuation as reported by the PCP.

### RESULTS

Of the 150 questionnaires sent to PCPs, the response rate was 93.3% with 140 questionnaires returned with complete information. Of these, 71 (94.7%) were returned for the group of aspirin past users and 69 (92.0%) were returned for the group of never users. Baseline characteristics of patients in the two study groups are shown in Table 1. There was a greater proportion of patients with obesity, diabetes, hypertension, and hypercholesterolemia among past users of low-dose aspirin than among never users. Over 70% of past low-dose aspirin users had received low-dose aspirin previously for primary CVD prevention. Among past users who received low-dose aspirin for secondary CVD prevention, the two most common indications were MI (26.3%) and IHD (26.3%).

#### Patients currently taking low-dose aspirin as reported by PCPs

The number of patients reported by the PCPs to be currently taking low-dose aspirin at the time they filled in the questionnaire (January to March 2014) is shown in Table 2 by low-dose aspirin exposure group (past and never users as ascertained from THIN). Three (4.2%) past users were reported by PCPs to be currently taking the drug. Of these three patients, aspirin had been obtained OTC (for primary CVD prevention) by one patient (this patient was aged 49 years). Among never users of low-dose aspirin, PCPs reported that two patients (2.9%) were currently using the drug, with one of these patients having obtained it as OTC medication (Table 2) (this patient was 72 years of age).

It should be reiterated that our group of past and never users were identified based on information available in THIN in September 2013, which represented

Table 1. Baseline characteristics of past and never users of low-dose aspirin identified from THIN

Characteristic	Past users of low-dose aspirin* N = 75 n (%)	Never users of low-dose aspirin N = 75 n (%)
Sex		
Men	35 (46.7)	46 (61.3)
Women	40 (53.3)	29 (38.7)
Smoking		
Non-smoker	27 (36.0)	36 (48.0)
Current	14 (18.7)	12 (16.0)
Past	34 (45.3)	27 (36.0)
BMI (kg/m <sup>2</sup> )		
15–19	2 (2.7)	2 (2.7)
20–24	19 (25.3)	23 (30.7)
25–29	21 (28.0)	30 (40.0)
≥30	32 (42.7)	19 (25.3)
Unknown	1 (1.3)	1 (1.3)
Diabetes	27 (36.0)	5 (6.7)
Hypertension	51 (68.0)	28 (37.3)
Hypercholesterolemia	25 (33.3)	17 (22.7)
Low-dose aspirin indication		
Primary CVD prevention	56 (74.7)	NA
Secondary CVD prevention	19 (25.3)	
Myocardial infarction <sup>†</sup>	5 (26.3)	NA
Unstable angina <sup>†</sup>	3 (15.8)	NA
Revascularization <sup>†</sup>	—	NA
Cerebrovascular disease <sup>†</sup>	4 (21.1)	NA
PAD <sup>†</sup>	2 (10.5)	NA
IHD unspecified <sup>†</sup>	5 (26.3)	NA

BMI, body mass index; CVD, cardiovascular disease; IHD, ischaemic heart disease; PAD, peripheral artery disease; THIN, The Health Improvement Network.

\*Past users of low-dose aspirin were defined as individuals whose last low-dose aspirin prescription finished at least 1 year before the time of sending the questionnaire.

<sup>†</sup>Percentages are among past users of low-dose aspirin who received aspirin for secondary CVD prevention.

the latest available data in THIN at the time of carrying out the study and which was before the time the PCPs filled in the questionnaires (January to March 2014). Since conducting this study, more recent data from THIN has become available (up to May 2014), which covers the period during which the PCPs filled the questionnaires. These data have shown that among the two past users who were reported by the PCP to be currently taking low-dose aspirin by prescription, these were indeed found to be current users in THIN (i.e., there were recorded prescriptions). Similarly, current use of low-dose aspirin by prescription was found for the single never user whom the PCP reported was currently using low-dose aspirin by prescription. In addition, for the single past user and the single never user for whom the PCP reported use of OTC low-dose aspirin, no low-dose aspirin prescriptions were found in the latest data from THIN for either patient.

Table 2. Number of patients (past and never low-dose aspirin users) reported by the PCP to be currently taking low-dose aspirin (at the time the PCP filled the questionnaire)

Information provided by the PCP (from the questionnaire)	Past users of low-dose aspirin* (identified from THIN) N = 71	Never users of low-dose aspirin (identified from THIN) N = 69
Patient currently using low-dose aspirin, n (%)		
Yes	3 (4.2)	2 (2.9)
No	65 (91.5)	62 (89.9)
Unknown	3 (4.2)	5 (7.2)
OTC use in patients currently using low-dose aspirin (n)		
Yes	1	1
No	2	1
Indication among patients taking low-dose aspirin, n (%)		
Primary CVD prevention	2	—
MI	1	—
IHD	—	2

CVD, cardiovascular disease; IHD, ischaemic heart disease; myocardial infarction, IHD, ischaemic heart disease; OTC, over-the-counter; PCP, primary care practitioner; THIN, The Health Improvement Network.

\*Past users of low-dose aspirin were defined as individuals whose last low-dose aspirin prescription finished at least 1 year before the time of sending the questionnaire.

*Patients who had previously taken low-dose aspirin as reported by PCPs.* As shown in Table 3, past use of low-dose aspirin was reported in 63 (88.7%) of past users (i.e., past use in THIN was confirmed by the PCP). All 63 patients had received their aspirin by prescription, with none having received it as OTC medication. Only two never users of low-dose aspirin (2.9%) were reported by the PCP to have been a past user, with one patient having obtained his or her aspirin OTC (Table 3) (this patient was aged 58 years).

#### *Indication for low-dose aspirin and reason for discontinuation reported by PCPs*

Among patients reported by the PCPs as having previously used low-dose aspirin, 57 (90.5%) had information regarding the indication for this previous use. The indication for this low-dose aspirin (which was all prescribed) was primary CVD prevention in 63.2% of patients and secondary CVD prevention (coronary diseases, cerebrovascular diseases, and peripheral artery disease) in 31.6% of patients (Table 4). Concordance in the indication obtained from the two data sources at the individual level is shown in the Supporting Information Table. Among patients where the indication reported by the PCP was primary prevention of CVD, approximately 90% had the same indication recorded in

Table 3. Number of patients (past and never low-dose aspirin users) reported by the PCP to have previously taken low-dose aspirin (at the time the PCP filled the questionnaire)

Information based on questionnaire	Past users of low-dose aspirin* (identified from THIN) N = 71 n (%)	Never users of low-dose aspirin (identified from THIN) N = 69 n (%)
Patients with previous use of low-dose aspirin		
Yes	63 (88.7)	2 (2.9)
No	3 (4.2)	57 (82.6)
Unknown	5 (7.0)	10 (14.5)
Patients with previous use of low-dose aspirin		
Prescribed	63 (100)	1 (1.5)
OTC use	0 (0)	1 (1.5)
Indication reported by the PCP	63 (88.7)	2 (3.0)
Primary CVD prevention <sup>†</sup>	36 (57.1)	—
Secondary CVD prevention <sup>†</sup>	27 (42.9)	1 (50.0)
Coronary diseases <sup>†‡</sup>	10 (15.9)	1 (50.0)
Cerebrovascular disease <sup>†</sup>	7 (11.1)	—
PAD <sup>†</sup>	1 (1.6)	—
Migraine <sup>†</sup>	1 (1.6)	—
Atrial fibrillation <sup>†</sup>	1 (1.6)	1 (50.0)
Chronic kidney disease <sup>†</sup>	1 (1.6)	—
Unknown <sup>†</sup>	6 (9.5)	—
Reasons for low-dose aspirin discontinuation reported by PCP <sup>†</sup>		
Adverse event	10 (15.9)	—
Gastrointestinal	6 (9.5)	—
Other bleeding	1 (1.6)	—
Anemia	2 (3.2)	—
Non-specified	1 (1.6)	—
Changed	6 (9.5)	1 (50.0)
antiplatelet or antithrombotic		
Warfarin	3 (4.8)	—
Not indicated	12 (19.0)	1 (50.0)
Unknown	35 (55.6)	—

CVD, cardiovascular disease; OTC, over-the-counter; PAD, peripheral artery disease; PCP, primary care practitioner; THIN, The Health Improvement Network.

\*Past users of low-dose aspirin were defined as individuals whose last low-dose aspirin prescription finished at least 1 year before the time of sending the questionnaire.

<sup>†</sup>Percentages shown are among the 63 patients who the PCP reported had used low-dose aspirin previously in the past user group and among the two patients who the PCP reported had used low-dose aspirin previously in the never user group.

<sup>‡</sup>This variable includes the following pathologies: myocardial infarction, unstable angina, chest pain, and ischaemic heart diseases.

THIN. Among the set of 57 reported previous users of low-dose aspirin, the indication as ascertained from THIN was 78.9% for primary CVD prevention and 21.1% for secondary CVD prevention (Table 4). The PCP-reported reasons for discontinuation of this previous aspirin therapy were as follows: treatment no longer indicated (19.0%), adverse events (15.9%), and alternative antiplatelet/anticoagulant treatment (9.5%);



Table 4. Indication for low-dose aspirin as obtained from both PCP questionnaires and THIN

	Low-dose aspirin treatment indication among patients reported to have previously used low-dose aspirin (from PCP questionnaires)	
	Information based on questionnaire	THIN database
	<i>N</i> = 57 <i>n</i> (%)	<i>N</i> = 57 <i>n</i> (%)
Primary CVD prevention	36 (63.2)	45 (78.9)
Secondary CVD prevention	18 (31.6)	12 (21.1)
Coronary diseases*	10 (17.5)	7 (12.3)
Cerebrovascular disease	7 (12.3)	3 (5.3)
PAD	1 (1.7)	2 (3.5)
Migraine	1 (1.7)	NA
Atrial fibrillation	1 (1.7)	NA
Chronic kidney disease	1 (1.7)	NA

CVD, cardiovascular disease; IHD, ischaemic heart disease; MI, myocardial infarction; PAD, peripheral artery disease; PCP, primary care practitioner; UA, unstable angina; THIN, The Health Improvement Network.

\*Includes MI, UA, chest pain, and IHD.

PCPs did not report reasons for discontinuation of therapy for 55.6% of patients.

#### OTC use of other medications reported by PCPs

Use of other commonly used medications obtained OTC among the 71 past users of low-dose aspirin and 69 never users for whom questionnaires were received is shown in Table 5. PCPs reported that 11 (15.5%) past users of low-dose aspirin were currently receiving PPIs as OTC medication (lansoprazole was the most commonly used; 81.2%), one patient (1.4%) was taking a H<sub>2</sub>RA as OTC medication, and four patients (5.6%) were taking NSAIDs as OTC medication. Among never users of low-dose aspirin, four patients (5.8%) were receiving PPIs as OTC medication and two patients (2.9%) were taking NSAIDs, while none were taking H<sub>2</sub>RAs as OTC medication.

Among the 11 past users of low-dose aspirin for whom the PCP reported OTC use of PPIs, 10 patients (90.9%) also had recorded prescriptions for a PPI. Among past users of low-dose aspirin reported to have received H<sub>2</sub>RA, all (100%) had recorded prescriptions for an H<sub>2</sub>RA; while for past users reported to have received NSAIDs as OTC medication, 75% had recorded NSAID prescriptions. Similarly among never users of low-dose aspirin, three of the four patients who were reported to have received PPIs as OTC medication had recorded prescriptions for PPIs. Of the two patients reported to have received NSAIDs as OTC medication, both

Table 5. OTC use of other common treatments as obtained from PCP questionnaires

	Past users of low-dose aspirin* (identified from THIN) <i>N</i> = 71	Never users of low-dose aspirin (identified from THIN) <i>N</i> = 69
PPIs		
No, <i>n</i> (%)	33 (46.5)	34 (49.3)
Yes, <i>n</i> (%)	11 (15.5)	4 (5.8)
Omeprazole <sup>†</sup> , <i>n</i> (%)	2 (18.2)	3 (75.0)
Lansoprazole <sup>†</sup> , <i>n</i> (%)	9 (81.2)	1 (25.0)
Unknown, <i>n</i> (%)	27 (38.0)	31 (44.9)
H <sub>2</sub> RA		
No, <i>n</i> (%)	41 (57.7)	32 (46.4)
Yes, <i>n</i> (%)	1 (1.4)	—
Ranitidine, <i>n</i>	1	—
Unknown, <i>n</i> (%)	29 (40.8)	37 (53.6)
NSAIDs		
No, <i>n</i> (%)	34 (47.9)	31 (44.9)
Yes, <i>n</i> (%)	4 (5.6)	2 (2.9)
Diclofenac, <i>n</i>	2	—
Ibuprofen, <i>n</i>	1	—
Etoricoxib, <i>n</i>	1	—
Piroxicam, <i>n</i>	—	1
Naproxen, <i>n</i>	—	1
Unknown, <i>n</i> (%)	33 (46.5)	36 (52.2)

H<sub>2</sub>RA, histamine-2 receptor antagonist; NSAIDs, non-steroidal anti-inflammatory drugs; OTC, over-the-counter; PPIs, proton pump inhibitors; PCP, primary care practitioner; OTC, over-the-counter; THIN, The Health Improvement Network.

\*Past users of low-dose aspirin were defined as individuals whose last low-dose aspirin prescription finished at least 1 year before the time of sending the questionnaire.

<sup>†</sup>Percentages shown are among the 11 patients who the PCP reported were using OTC PPIs in the past user group and among the four patients who the PCP reported were using OTC PPIs in the never user group.

also had recorded prescriptions for NSAIDs. However, caution should be applied when interpreting these estimations as they are based on very small numbers.

## DISCUSSION

This novel study aimed to validate the low-dose aspirin prescribing information recorded in THIN database. We found the level of potential misclassification of low-dose aspirin exposure in THIN due to unrecorded OTC use to be minimal. From the information provided by the PCPs, only one patient in our sample of past low-dose aspirin users (discontinuers) and one patient in our sample of never low-dose aspirin users were misclassified into these groups due to unrecorded current use of OTC low-dose aspirin.

In the UK, health care is easily accessed and prescriptions are free for people aged 60 years or more — the age range of the patient population in which low-dose aspirin is most commonly used and a factor that would encourage prescription. Younger patients have been

found previously to be significantly more likely than older patients to obtain low-dose aspirin OTC.<sup>18</sup> A previous study comparing aspirin prescription records in the Clinical Practice Research Datalink GOLD (a similar UK database to THIN) to patient self-report found that the majority of chronic aspirin use was captured by prescription records.<sup>19</sup> Two other regional studies carried out in previous decades among patients with CVD in UK general practice reported that around 20% of patients who were taking aspirin had obtained it as OTC medication.<sup>18,20</sup> While another study, albeit nearly 20 years ago, reported this proportion to be much higher with 40% of aspirin users reporting to have received their medication OTC,<sup>21</sup> although it was not specified whether this was for short-term use for analgesic purposes or long-term use of low-dose therapy for CVD prophylaxis. In a more recent survey of nearly 500 patients in Australia, only 2.1% reported OTC antithrombotic use.<sup>22</sup>

At the group level, the PCP-reported indication for low-dose aspirin in our sample of patients was found to have a high level of concordance with the indication recorded in THIN. The slightly higher proportion of patients with an indication of primary CVD prevention in THIN could be explained by allocation of patients into two indication categories (primary or secondary CVD prevention) compared with the four extra indications reported by the GPs in the open-ended question in the questionnaire; 7% of patients were reported to have indications other than CVD prevention. Among patients receiving low-dose aspirin for secondary CVD prevention in this study (identified from THIN), the proportion of patients in whom the indication was either coronary heart disease or cerebrovascular disease is consistent with a previous study in THIN carried out among a large sample of aspirin users and in which the indication was obtained following manual review of patients' electronic medical records.<sup>23</sup>

Non-adherence to low-dose aspirin remains an important public health concern being associated with poor outcomes.<sup>1,2,10</sup> The reason for low-dose aspirin discontinuation was not reported by PCPs for over half of the past users (discontinuers) in this study; further studies are warranted to evaluate this scenario. Among past users with a reported reason for discontinuation, the reason was reported by the PCP as "adverse events" in 16%. Because discontinuation due to adverse events is more likely to be recorded by the PCP, we believe that the majority of past users with an unreported reason for aspirin discontinuation would have stopped treatment due to non-safety concerns. This would be in line with our findings from previous research in larger cohorts of aspirin users in THIN, in which non-safety

concerns — mostly non-adherence — were by far the most commonly recorded reason for aspirin discontinuation.<sup>1,2,24</sup> It should be noted that the reasons for aspirin discontinuation in these previous studies were ascertained through manual review of patients' electronic medical records.

When using electronic medical records for the evaluation of a medication, it is important to obtain both accurate exposure and outcome data in order to obtain valid estimates of effect. For instance, non-differential misclassification of an exposure to a medication in a case-control study will bias the risk estimate towards an underestimation of the true effect. Similarly, descriptive studies of medication use are reliant on accurate exposure data for a true understanding of their use. It is important to identify true users of a medication but even more essential that false negatives are identified. THIN database has been used for several pharmacoepidemiology and drug utilization studies, including studies on patterns of low-dose aspirin use<sup>11,12</sup> and its effects on clinical outcomes.<sup>1-3,5,10,24</sup> The very small proportion of false negatives found in our study strengthens the findings of these studies.

To the best of our knowledge, there have been no other validation studies of low-dose aspirin data recorded in THIN. A strength of our study is that THIN is a population-based database representative of the UK population.<sup>17</sup> Limitations of our study include the small sample size and the possibility that patients in our sample did not report OTC use to their doctor, and therefore this information was not recorded in their patient record (either paper or electronic). However, we feel the impact of any such misclassification would be minimal and especially unlikely among patients receiving aspirin for secondary CVD prevention who are more likely to be in regular contact with their PCP. Elwood *et al.*<sup>25</sup> reported that 97% of patients with a previous vascular event and taking aspirin did so on the advice of their doctor, thereby implying that communication between the PCP and the patient is not generally lacking in this group of patients. Misclassification of low-dose aspirin exposure is possible if a prescription was issued in secondary care and this information was not later transferred to their primary care records. However, we believe few patients would have their aspirin exposure misclassified by this factor because low-dose aspirin is predominantly prescribed in primary care. It is also possible that there could have been some misclassification of current and past users of low-dose aspirin in THIN owing to patients not adhering to their medication and not reporting this to their PCP.

In conclusion, our findings demonstrate the utility of THIN database for studies of low-dose aspirin use and

its effects. It reinforces the validity of previous studies of low-dose aspirin carried out using THIN, which include both studies of utilization,<sup>11,12,23</sup> and those evaluating associations with clinical outcomes, including MI,<sup>1,10</sup> stroke,<sup>2,10</sup> upper gastrointestinal bleeding,<sup>4,10,24</sup> and colorectal cancer.<sup>3</sup> We have also shown that THIN is an appropriate data source for the study of certain other medications that can be obtained either by prescription or OTC, such as PPIs and NSAIDs. For the evaluation of medications not included in our study, such as statins, further investigation is warranted to draw conclusions about the utility of THIN.

## CONFLICT OF INTEREST

This work was supported by Bayer Pharma AG. Montse Soriano Gabarró is a salaried, full-time employee of Bayer Pharma AG, the sponsor of the study. Lucía Cea Soriano and Luis A. García Rodríguez work for CEIFE, which has received a research grant from Bayer Pharma AG. Dr García Rodríguez has also served as a consultant and advisory board member for Bayer Pharma AG.

## KEY POINTS

- This study found the level of potential misclassification of low-dose aspirin exposure in The Health Improvement Network due to unrecorded over-the-counter use to be minimal
- Our findings show the utility of The Health Improvement Network database for clinical studies of low-dose aspirin.

## ETHICS STATEMENT

The study protocol was reviewed and approved by an independent scientific review committee (reference number 12-044V).

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