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ORIGINAL ARTICLE

Validation of self-reported medication use applying untargeted mass spectrometry-based metabolomics techniques in the Rhineland study

Nersi Alaeddin[1] | Julia C. Stingl[2] | Monique M. B. Breteler[1,3] | Folgerdiena M. de Vries[1]

[1]Population Health Sciences, German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany

[2]Institute of Clinical Pharmacology, University Hospital of RWTH Aachen, Aachen, Germany

[3]Institute for Medical Biometry, Informatics and Epidemiology (IMBIE), Faculty of Medicine, University of Bonn, Germany

Correspondence
Folgerdiena M. de Vries, PhD, Deutsches Zentrum für Neurodegenerative Erkrankungen e.V., In der Helmholtz-Gemeinschaft, Venusberg-Campus 1, Building 99, 53127, Bonn, Germany.
Email: dianna.devries@dzne.de

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Aims: To assess the validity of self-reported continuous medication use with drug metabolites measured in plasma by using untargeted mass spectrometric techniques.

Methods: In a population-based cohort in Bonn, Germany, we compared interview-based, self-reported medication intake with drug-specific metabolites measured in plasma (based on participants who completed their study visits between March 2016 and February 2020). Analyses were done stratified by sex and age (<65 years *vs* ≥65 years). Cohen's kappa (κ) statistics with 95% confidence intervals (CI) were calculated.

Results: A total of 13 drugs used to treat hypertension, gout, diabetes, epilepsy and depression were analysed in a sample of 4386 individuals (mean age 55 years, 56.1% women). Eleven drugs showed almost perfect agreement (κ > 0.8), whereas sitagliptin and hydrochlorothiazide showed substantial ($\kappa = 0.8$, 95% CI 0.71–0.90) and moderate agreement ($\kappa = 0.61$, 95% CI 0.56–0.66), respectively. Frequency of use allowed sex- and age-stratified analyses for eight and nine drugs, respectively. For five drugs, concordance tended to be higher for women than for men. For most drugs, concordance was higher among individuals aged ≥65 years than among individuals aged <65 years, but these age-related differences were not statistically significant.

Conclusion: High concordance rates between self-reported drug use and metabolites measured in plasma suggest that self-reported drug use is reliable and accurate for assessing drug use.

KEYWORDS
mass spectrometry, metabolomics, molecular epidemiology, pharmacoepidemiology, self-reported data, validity

The authors confirm that the Principal Investigator for this paper is Monique M.B. Breteler.

1 | INTRODUCTION

Large population-based cohort studies often depend on self-reported medication use to determine drug exposure. The quality of self-reported data is frequently questioned because it depends on the accuracy and truthfulness of the participant and is prone to several forms of bias.[1–6] Studies showed no difference in the ability to recall medication use by sex, but reported a decrease with age.[7–9] Another method of assessing medication use that is not expected to be influenced by patient characteristics is the use of secondary data from electronic medical records (EMRs). This method is commonly considered a gold standard for determining medication exposure.[1,10–16] However, it can be questioned whether EMRs indeed reflect actual medication use. EMRs are usually based on prescription data from general practitioners or dispensing data from public pharmacy records. Consequently, medication dispensed in hospitals is often incomplete in these records. Additionally, approximately 40% of patients fail to adhere to their medication as prescribed,[17] which is also not reflected in EMRs but can be addressed in self-reported medication use. Furthermore, self-reported medication use has the advantage of including over-the-counter (OTC) medication and dietary supplements.

Several studies validated self-reported medication use with EMRs.[10–16,18–20] The findings of these studies have been conflicting, showing both over- and underreporting, and levels of agreement often varied across medication classes. High concordance rates were reported for cardiovascular drugs ($\kappa > 0.75$),[10,12,16] while results were inconsistent for drugs prone to stigmatization bias, such as psycholeptics or mood stabilizers (concordance rates ranging from 0.52 to 0.75).[10–12,19] It is unknown whether lower concordance in, for example, psychotropic drugs is due to people giving socially desirable answers or that EMRs do not reflect actual intake.

In general, it is questionable whether medication use extracted from EMRs should be favoured over self-reported medication use. Studies comparing multiple drug metabolites measured in blood using liquid chromatography–tandem mass spectrometry techniques (LC–MS/MS) with EMRs reported huge discrepancies between the two.[21,22] In a patient cohort of 821 US adults, prescription records were compared with a drug metabolite panel consisting of 38 different drugs using an LC–MS/MS assay. Only 46% of the drugs assessed were detected and reported. Of the remaining drugs, 23% were detected in blood but not listed in the prescription records, whereas 30% were present in the prescription records but not detected in blood.[21] Another US study reported discrepancies between medical records and measured metabolites in 63% of the patients.[22]

Depending on a sufficiently long half-life in blood, drug metabolites measured in plasma can provide an unbiased estimate of actual drug intake and can be more appropriate than EMRs to validate self-reported medication use. A study using an untargeted metabolomics approach found good concordance between self-reported acetaminophen use and blood plasma metabolites but poor concordance for ibuprofen.[23] Indeed, validating self-reported use with medication metabolites might not be ideal for analgesics, which are often used irregularly on the occurrence of symptoms and have a short half-life. For drugs used regularly for chronic conditions, validation of self-reported medication use with drug metabolites measured in plasma would be more appropriate.

What is already known about this subject

- The quality of self-reported medication data is frequently questioned because it depends on the accuracy and truthfulness of participants.
- Studies validating self-reported medication use with electronic medical records showed conflicting results with both over- and underreporting.
- Validating self-reported medication use with drug metabolites measured in plasma would be more appropriate.

What this study adds

- For most drugs, including antidepressants, the agreement between self-reported chronic medication use and drug metabolites measured in plasma was almost perfect.
- Within our study self-reported drug intake was a reliable and accurate method for assessing medication exposure.

In this study, we aimed to assess the validity of self-reported continuous medication use with drug metabolites measured in plasma with untargeted mass spectrometry-based metabolomics. Furthermore, we assessed whether the validity of self-reported medication use depended on sex or age.

2 | METHODS

2.1 | Study design and setting

We used baseline data from the Rhineland Study, an ongoing prospective population-based cohort study in Bonn, Germany. This single-centre study started recruitment in 2016 and invites all residents (≥30 years) from two geographically defined areas in Bonn. Contact details of eligible participants are provided by the municipality. Participation is possible on invitation only, regardless of current health status. Those unable to sufficiently understand the informed consent are excluded. All participants undergo in-depth phenotyping, including assessment of cardiovascular measures, brain imaging, cognitive testing, neurologic functioning, untargeted metabolomic profiling in plasma and medication use. Approval to undertake the study was granted by the ethics committee of the University of Bonn, Medical Faculty. This study is performed according to the recommendations of the International Council for Harmonisation (ICH) and the Good Clinical Practice (GCP) standards. We obtained written informed consent

from all participants in accordance with the Declaration of Helsinki. Participants were not offered any financial incentives.

2.2 | Medication data collection

Participants were requested to bring the original packages of all drugs (including OTC drugs, excluding homeopathic drugs) and prescribed supplements used currently or used *as needed* during the last year.[24] As-needed OTC drugs taken for <10 days in the preceding year were not registered. Regular drug use was defined as use at a specific dosing interval, eg, daily, every other day, weekly, without regard to symptoms. Drug use on the occurrence of symptoms was classified as as-needed use. Medication data was assessed interview-based, using a software instrument for database-assisted online collection of medication data (Instrument zur Datenbank gestützten Online-Erfassung von Medikamenten, IDOM).[25] The Research Institute of the Federal Association of Regional Statutory Health Insurance Funds in Germany (Wissenschaftliches Institut der Ortskrankenkassen, WIdO) provides a database containing information on all drugs available on the German market, which is linked to the IDOM software.[26] The name, dosage, Anatomical Therapeutic Chemical (ATC) code,[27] type of use (regularly or as needed) and current prescription status were registered for each preparation.

2.3 | Metabolomics measurements

Drug metabolites were measured in plasma using an untargeted analytical approach (described in detail in section 2.4), which allows the identification of up to 44 different drugs from a reference library (Metabolon Inc., Durham, USA). This in-house reference library contains authenticated standards with retention index, mass-to-charge ratio (m/z) and MS/MS spectral data for each metabolite.[28] The panel contains metabolites of commonly used drugs that are representative of a variety of drug classes (Table A1). Blood samples were collected in the morning after a minimum of 10 hours of fasting using a standard operating procedure. Plasma originated from blood collected in ethylenediaminetetraacetic acid (EDTA)-containing vacutainers. Samples were maintained at −80 °C and accessioned into a laboratory information management system (LIMS) to track all results, samples and derived aliquots. All samples were analysed via ultrahigh-performance liquid-phase chromatography and separation coupled with tandem mass spectrometry.[28–30] Raw data were extracted, and the characteristic chromatographic peaks and relative ion concentrations of the detected metabolites were determined for each sample. Subsequently, the spectrometry data were analysed to identify and quantify individual components using the quantify individual components in a sample method.[31] Here, ions for a given metabolite are determined from LC–MS/MS data based on retention time, mass ion intensity and covariance of ion data across the entire sample set. Relative metabolite levels were computed by using the area under the curve. Retention index and mass-to-charge ratio (m/z) for the investigated metabolites are provided in Table A2. Participants were considered users of a specific drug if the respective drug metabolite was detected. Missing values were considered to mirror quantities below levels of detection and were therefore classified as nonusers of the specific drug.

2.4 | Ultrahigh-performance liquid chromatography-tandem mass spectroscopy

We use an LC-MS-based untargeted metabolomics approach for analysing the drug metabolites. All analyses used a Waters ACQUITY ultra-performance liquid chromatograph (UPLC) (Waters Limited, Mississauga, ON, Canada), a Thermo Scientific Q-Exactive high-resolution mass spectrometer interfaced to a heated electrospray ionization source (HESI-II) and an Orbitrap mass analyser with a mass resolution of 35 000 (Thermo Fisher Scientific, Waltham, Massachusetts, USA).[28,32] Sample extracts were dried and reconstituted in solvents compatible with each of the four methods (i-iv) described below. Each reconstitution solvent contained a set of standards (fixed concentrations) to guarantee consistency of injection and chromatography. (i) One aliquot was analysed under acidic positive-ion conditions and chromatographically optimized for more hydrophilic compounds. The extract was gradient eluted from a C18 column (Waters UPLC BEH C18, 2.1 × 100 mm, 1.7 μm) with water and methanol containing 0.05% perfluoropentanoic acid and 0.1% formic acid. (ii) Another aliquot was analysed under acidic positive-ion conditions and chromatographically optimized for hydrophobic compounds. Here, the extract was gradient eluted with methanol, acetonitrile, water, 0.05% perfluoropentanoic acid and 0.01% formic acid from the same C18 column mentioned above and run at a higher overall organic content. (iii) The third aliquot was analysed using basic negative-ion-optimized conditions using a separate C18 column. Basic extracts were gradient eluted from the column with water and methanol with 6.5 mM ammonium bicarbonate (pH 8). (iv) The fourth aliquot was analysed by negative ionization following elution from a HILIC column (Waters UPLC BEH Amide, 2.1 × 150 mm,1.7 μm) using a gradient consisting of water and acetonitrile with 10 mM ammonium formate (pH 10.8).

2.5 | Selection criteria of included drugs

Of all drugs detected with the metabolomics panel, we included only those (i) that were used for long-term conditions and used regularly, (ii) that were self-reported by ≥15 participants and (iii) for which we expected a priori that the available drug metabolites would be appropriate for validation of self-reported drug use based on the pharmacokinetic properties of the drug (assessment by two pharmacists). A total of 75 drug metabolites associated with 44 different drugs (Table A1) can potentially be detected by the metabolomics panel. Of these drugs, we excluded 23 because they are not typically used regularly and six because fewer than 15 participants in our population reported regular use. For the remaining 15 drugs, we assessed

TABLE 1 Selection of drugs based on pharmacokinetic characteristics

Drug class	Drug	t_{max} (h)	Bioavailability (%)	Active metabolite	Measured metabolite(s)	Plasma elimination $t_{½}$ (h) of measured metabolite(s)	Included
Antihypertensive	Enalapril	1	40	Enalaprilat	Enalapril	<1	×
	Hydrochlorothiazide	2–5	70	Excreted unchanged	HCT	6–8	✓
	Metoprolol	1-2	35-50	Metoprolol	(a) Metoprolol (b) Metoprolol acid	3–5	✓
	Candesartan	3-4	14	Candesartan	Candesartan	9	✓
	Olmesartan	2	25.6	Olmesartan	Olmesartan	10–15	✓
	Valsartan	2-4	23	Valsartan	Valsartan	9	✓
Uricostatic	Allopurinol	1.5	67	Oxypurinol	(a) Allopurinol (b) Oxypurinol	18–43	✓
Antihyperglycemic	Metformin	2.5	30-60	Excreted unchanged	Metformin	5	✓
	Sitagliptin	1–4	87	Sitagliptin	Sitagliptin	12	✓
Antiepileptic	Gabapentin	2–3	60	No metabolization	Gabapentin	5–7	✓
Antidepressant	Citalopram	3	80	Desmethylcitalopram	(a) Citalopram-*N*-oxide (b) Citalopram propionate (c) Desmethylcitalopram (d) Escitalopram	35	✓ Combined with escitalopram
	Escitalopram	3–4	80	Desmethylcitalopram	(a) Citalopram-*N*-oxide (b) Citalopram propionate (c) Desmethylcitalopram (d) Escitalopram	35	✓ Combined with citalopram
	Fluoxetine	6–8	72	Norfluoxetine	Fluoxetine	96–144	✓
	Venlafaxine	2–3	40–45	O-desmethylvenlafaxine	(a) Venlafaxine (b) *O*-desmethylvenlafaxine	5–11	✓
Antipsychotic	Quetiapine	1	100	N-desalkylquetiapine	(a) Quetiapine (b) *N*-desalkylquetiapine	7–12	✓

whether their pharmacokinetic properties were suitable for validating self-reported drug use (Table 1), and we excluded enalapril after this assessment. The panel measures enalapril, rather than the active metabolite enalaprilat. Since enalapril is a rapidly transformed prodrug (plasma elimination $t_{½}$ < 1 hour), we expected many false positives. Based on our pharmacokinetic assessment, we also combined citalopram and escitalopram. Escitalopram is the therapeutically active *S*-enantiomer of the racemic mixture citalopram, therefore differentiation between the intake of both drugs via the metabolomic panel is not possible. Ultimately, we analysed 12 individual drugs and the combination of citalopram and escitalopram (Table 1).

2.6 | Study population

This cross-sectional study was conducted on the first 5000 participants of the Rhineland Study who completed their study visits between March 2016 and February 2020. Analyses were based on 4500 participants for whom we measured drug metabolites in plasma. Of these, we had to exclude 114 participants because (i) metabolomics data were incomplete (n = 29), (ii) self-reported medication data were incomplete (n = 71) and (iii) use of the respective drug was reported as needed (n = 14). The analytical sample comprised 4386 individuals (women, n = 2459; men, n = 1927; <65 years, n = 3216; ≥65 years, n = 1170).

2.7 | Statistical analysis

Descriptive statistics are presented for women and men. Groups were compared using chi-square tests (categorical variables) and ANOVA tests (continuous variables). We assessed concordance between self-reported medication intake and drug metabolites measured in plasma. Participants' self-report data were classified as (i) *true positive* (metabolite detected and self-reported use), (ii) *true negative* (metabolite not detected and no self-reported use), (iii) *false positive* (metabolite not detected but self-reported use) or (iv) *false negative* (metabolite detected but no self-reported use). Concordances between self-reported drug use and measured metabolites were calculated using Cohen's kappa (κ). The kappa statistic measures the extent of inter-rater agreement. Kappa values were classified as (i) ≤0.4 *poor to fair agreement*, (ii) 0.41–0.6 *moderate agreement*, (iii) 0.61–0.8 *substantial agreement* and (iv) >0.8 *almost perfect agreement*.[33] All κ values are presented with 95% confidence intervals (CI). Additional analyses were performed stratified for sex and age (<65 *vs* ≥65 years), when the number of users in each subgroup was ≥15. All statistical analyses were performed using R version 3.6.1.

2.8 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[34]

3 | RESULTS

3.1 | General characteristics of the study population

The characteristics of the analytical sample of 4386 individuals are presented in Table 2. Among included participants, the mean age was 55.0 years (standard deviation [SD] 14.0 years, range 30–95) and 26.7% (n = 1170) of the individuals were ≥65 years. Included participants were younger (P < .001) than those excluded (mean age 59.9 years, SD 13.7 years, range 30–87). The ratio of women to men was higher (P < .001) in included participants (56.1% women, n = 2459) compared to those excluded (45.6% women, n = 52). On average, participants used 2.1 drugs (SD 2.6 drugs) and individuals aged ≥65 years (3.8 drugs, SD 3.3) used significantly (P < .001) more drugs than those aged <65 years (1.7 drugs, SD 2.1). Elevan of the 13 drugs analysed are among the top 40 most frequently, regularly used drugs in the Rhineland Study (Table A3).

3.2 | Accuracy of self-reported medication use

Of the 13 drugs analysed, 11 showed an almost perfect agreement (κ > 0.8) between self-reported medication use and metabolites measured in plasma (Table 3). For sitagliptin, the agreement was only slightly lower, with κ = 0.80 (46 users, 95% CI 0.71–0.90). For hydrochlorothiazide, the concordance was only 0.61 (355 users, 95% CI 0.56–0.66), as we did not detect metabolites in 187 self-reported users.

Concordance rates for antihypertensive drugs other than hydrochlorothiazide were comparable to concordance rates for the included antidepressants and quetiapine (Table 3). The concordance rates of antihyperglycemic medications tended to be lower (κ < 0.90) than those of antihypertensives, antidepressants and quetiapine, but still showed almost perfect/substantial concordance.

We performed sex-stratified analyses for drugs from each included drug class, except for gabapentin (Figure 1). For five of eight of these drugs, concordance was higher for women than men. There was no pattern with respect to drug classes. A statistically significant difference between men and women was observed only for allopurinol, with higher concordance in men (women, 15 users, κ = 0.68, 95% CI,0.52–0.83; men, 77 users, κ = 0.89, 95% CI 0.84–0.95). Detailed results on concordance rates stratified by sex can be found in Table A4.

We performed age-stratified analyses for drugs from each included drug class, except for gabapentin (Figure 2). Concordance was higher for seven of nine drugs in individuals ≥65 years compared to individuals aged <65 years. However, in all cases the 95% CIs of

TABLE 2 Descriptive characteristics of the population: total sample and stratified for sex

	Total sample	Missing (%)	Women	Men	*P* value
Number of participants, n (%)	4386		2459 (56.1)	1927 (43,9)	<.001
Age in years, M (SD)	55.0 (14.0)	0.0	54.8 (13.7)	55.2 (14.4)	.315
Age groups		0.0			.069
< 65 years	3216 (73.3)		1830 (74.4)	1386 (71.9)	
≥ 65 years	1170 (26.7)		629 (25.6)	541 (28.1)	
Education, n (%)		0.8			<.001
Low	81 (1.9)		63 (2.6)	18 (0.9)	
Middle	1950 (44.8)		1214 (49.8)	736 (38.5)	
High	2319 (53.3)		1159 (47.6)	1160 (60.6)	
Smoking, n (%)		4.0			<.001
Never	1992 (47.3)		1186 (50.3)	806 (43.5)	
Former	1701 (40.4)		901 (38.2)	800 (43.2)	
Current	519 (12.3)		273 (11.6)	246 (13.3)	
BMI (kg/m^2), M (SD)	25.9 (4.5)	0.5	25.4 (4.8)	26.5 (4.0)	<.001
Diabetes, n (%)	223 (5.1)	0.8	88 (3.6)	135 (7.0)	<.001
Hypertension, n (%)	1625 (37.6)	1.4	808 (33.4)	817 (42.8)	<.001
Hypercholesterolemia, n (%)	1693 (38.9)	0.8	944 (38.7)	749 (39.2)	.779
Polypharmacy, n (%)					<.001
All	582 (13.3)	0.0	340 (13.8)	242 (12.6)	
< 65 years	231 (7.2)		142 (7.8)	89 (6.4)	
≥ 65 years	351 (30.0)		198 (31.5)	153 (28.3)	
Average number of prescribed drugs, M (SD)		0.0			<.001
All	2.1 (2.6)		2.3 (2.6)	1.8 (2.7)	
< 65 years	1.4 (2.0)		1.7 (2.1)	1.1 (1.8)	
≥ 65 years	3.8 (3.3)		3.9 (3.1)	3.8 (3.5)	

Note: Education based on International Standard Classification of Education (low, lower secondary education or below; middle, upper secondary education to undergraduate university level; high, postgraduate university study). Diabetes based on current antidiabetic drug use/glycated haemoglobin (Hba1c) (no diabetes <6.5%, diabetes ≥6.5%) measured in fasting morning blood.

Hypertension based on measured mean systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, and/or antihypertensive drug use (irrespective of blood pressure levels). Hypercholesterolemia based on self-report. Polypharmacy defined as regular use of ≥5 prescribed drugs and supplements.

Abbreviations: BMI, body mass index; M, mean; n, number; SD, standard deviation.

the κ values overlapped, indicating no significant age-related differences. Detailed results on concordance rates stratified by age can be found in Table A5.

4 | DISCUSSION

We validated self-reported medication intake with drug metabolites measured in plasma with untargeted mass spectrometry-based metabolomics techniques in a general population (≥30 years). We included 13 drugs commonly used to treat hypertension, diabetes, depression, gout and epilepsy. We found almost perfect agreement rates ($\kappa > 0.8$) for 11 out of the 13 drugs analysed. Although psychoactive drugs are considered to be prone to stigmatization bias, we found an almost perfect agreement for all included antidepressants and quetiapine with concordances of $\kappa > 0.9$. Allopurinol was the only drug for which we observed significant sex differences, with higher concordance in men compared to women. There were no significant differences in concordance rates between younger and older age groups. The high concordance between self-reported medication use and measured drug metabolites suggests that interview-based self-reported medication data is a reliable and accurate method to assess regular drug intake, regardless of drug class, age and sex.

The diuretic hydrochlorothiazide showed the lowest concordance ($\kappa = 0.61$) between self-reported drug intake and measured metabolites. This was primarily due to a high number of false positives (187 of 355 regular self-reported users), meaning individuals reported taking hydrochlorothiazide but no metabolites were detected. Frequent urination is often a consequence of taking diuretics. Therefore, a possible explanation may be that participants did not take their diuretic when going out for the day to participate in our study. We do

TABLE 3 Concordance between self-reported drug use and measured metabolites with kappa (κ) values (95% CI)

Drug class	Drug	Regular users	TP	FP	TN	FN	Cohen's kappa (κ) (95% CI)
Antihypertensive	Hydrochlorothiazide	355	168	187	4023	8	0.61 (0.56–0.66)
	Metoprolol	101	92	9	4265	20	**0.86 (0.81–0.91)**
	Candesartan	279	269	10	4103	4	**0.97 (0.96–0.99)**
	Olmesartan	38	35	3	4348	0	**0.96 (0.91–1.00)**
	Valsartan	98	94	4	4284	4	**0.96 (0.93–0.99)**
Uricostatic	Allopurinol	92	85	7	4271	23	**0.85 (0.79–0.90)**
Antihyperglycemic	Metformin	109	89	20	4274	3	**0.88 (0.84–0.93)**
	Sitagliptin	46	31	15	4340	0	0.80 (0.71–0.90)
Antiepileptic	Gabapentin	19	14	5	4366	1	**0.82 (0.68–0.96)**
Antidepressant	(Es-) citalopram	90	86	4	4283	13	**0.91 (0.86–0.95)**
	Fluoxetine	19	19	0	4363	4	**0.90 (0.81–1.00)**
	Venlafaxine	49	47	2	4334	3	**0.95 (0.90–0.99)**
Antipsychotic	Quetiapine	16	16	0	4368	2	**0.94 (0.86–1.00)**

Note: Kappa values in bold show an almost perfect agreement (κ > 0.8).
Abbreviations: CI, confidence interval; FN, false negative (metabolite detected but no self-reported use); FP, false positive (metabolite not detected but self-reported use); TN, true negative (metabolite not detected and no self-reported use); TP, true positive (metabolite detected and self-reported use).

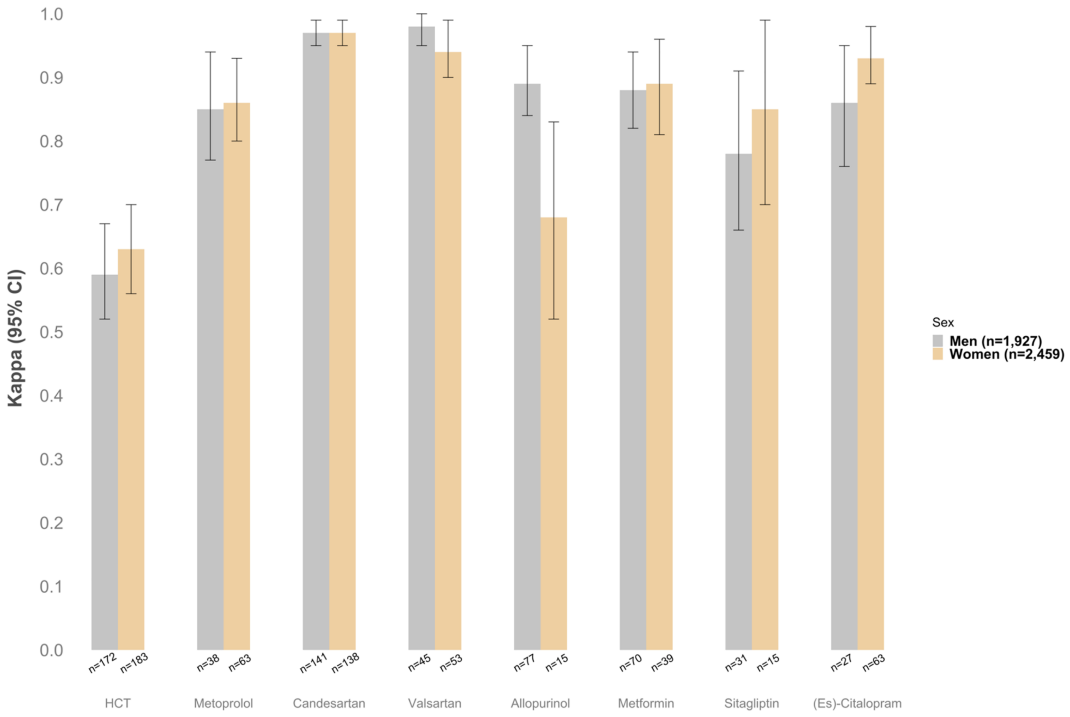

FIGURE 1 κ values with 95% CI of self-reported drug use *vs* drug metabolites measured in plasma, stratified for sex. n, number of drug users

not anticipate that hydrochlorothiazide degradation played a role in our samples because we detected hydrochlorothiazide in the longest-stored (>21 months) samples from low-dose users.

The concordance rate for sitagliptin was $\kappa = 0.80$. This borderline perfect agreement (κ > 0.8) was due to 15 false positives who reported medication intake but the drug metabolites were not detected. Because blood samples were collected before breakfast, it is likely that the last sitagliptin intake of most participants was more than 24 hours ago. Considering the elimination $t_{½}$ is 12 hours, this could explain why sitagliptin was not detected in some individuals.

Differences in concordances between older and younger age groups were small and nonsignificant, but generally higher in older age groups (≥65 years) compared to younger individuals (<65 years). This is consistent with the findings of Sediq et al[12] and contradicts the

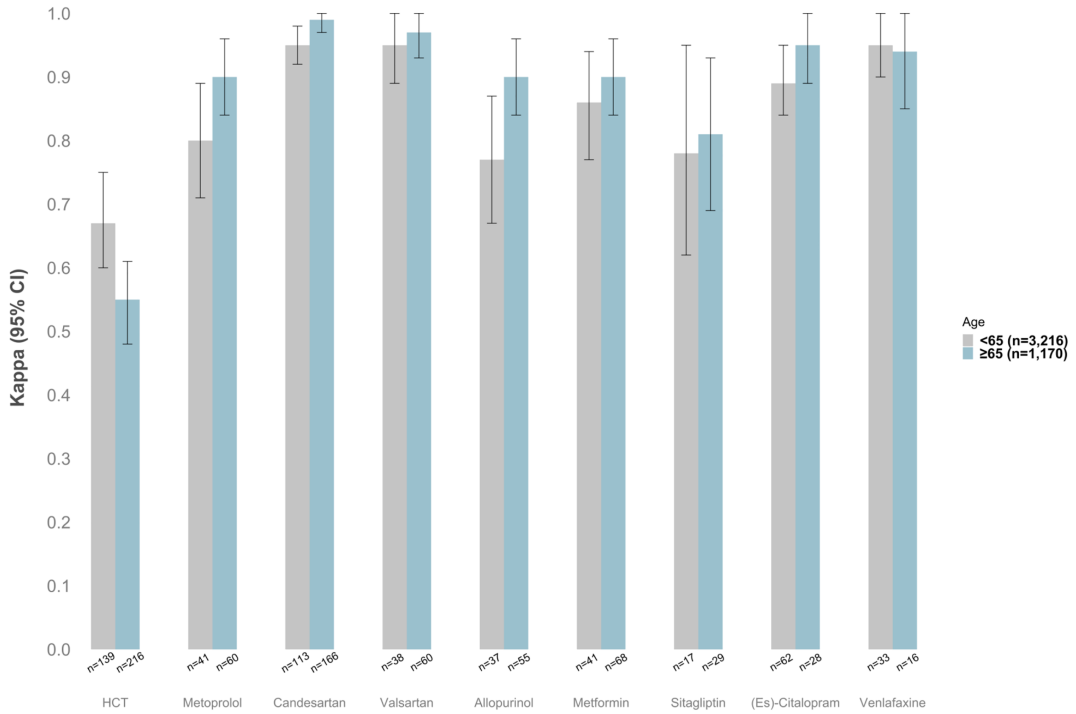

FIGURE 2 κ values with 95% CI of self-reported drug use *vs* drug metabolites measured in plasma, stratified for age. n, number of drug users

common assumption that the ability to recall medication use decreases with age as a result of cognitive decline and higher and more complex medication use.[35,36] Consistent with previous studies, we observed no effect of sex on concordance rates; we found only a significantly higher concordance in men compared to women for allopurinol.[11,12,16] However, there was a large difference in the prevalence of allopurinol use, with 77 users in men versus 15 in women.

Concerns regarding the accuracy of self-reported medication use mostly relate to the reliability of reporting certain drug classes vulnerable to stigmatization bias, such as antidepressants. While most studies validating self-reported antidepressant use with EMRs found concordance below 0.63,[10–12] some also reported good concordance.[13] In our study, we were able to analyse the validity of four antidepressants (citalopram/escitalopram, fluoxetine, venlafaxine) and one antipsychotic drug (quetiapine). For all of these drugs, we found concordance rates of ≥0.9, which may indicate that (i) the self-reported data collected in our study are of better quality than self-reported data from other studies and/or (ii) self-reported medication use better reflects actual intake than EMRs. It has been reported that more than 25% of individuals who are prescribed antidepressants for the first time decline treatment; they either do not start treatment or do not persist with antidepressant use for more than 2 weeks, which may result in inaccurate EMRs.[37]

We also found generally similar or even higher concordance rates compared with previous studies comparing self-reported medication use with EMRs.[10–12,16,19] As mentioned before, this may suggest that lower concordances are not due to inaccuracies in self-reported medication use but to inaccuracies in EMRs. Studies comparing multiple drug metabolites measured in blood using LC–MS/MS techniques with EMRs reported high rates of discrepancies between the two.[21,22] Even antihypertensive drugs, which are not prone to misuse, were not prescribed in 14–26% of cases where they were detected, suggesting that EMRs can be incomplete.[22] This can also be deduced from findings of a Dutch study comparing self-reported medication use with prescription records that unexpectedly found overreporting, ie, the drug was self-reported but not listed in prescription records.[12]

The strength of our study is that we validated self-reported medication use with metabolites measured in plasma, which is more reflective of actual drug use than EMRs. Furthermore, our data on self-reported medication use were assessed in a manner comparable to the brown bag method. This method is designed to provide a more complete overall picture of an individual's current medication profile compared to pharmacy records.[38,39] However, it is unclear whether self-reported data based on self-administered questionnaires, which are less time-consuming, are of the same quality. Another strength is that we were able to assess concordances for drugs prone to stigmatization bias, such as antidepressants, as well as for drugs not susceptible to stigma, such as antihypertensives. Although we were able to assess concordance rates for drug classes at high risk for stigmatization bias, we were unable to assess medication classes often dispensed in hospitals. For drugs dispensed in hospitals, EMRs might not be a good source for assessing exposure, and the quality of self-reported intake of those drugs is unclear. A limitation of our study is that we could not select the drugs according to their frequency of use. Nevertheless, 11 of the 13 drugs analysed were among the top 40 most frequently, regularly used drugs in the Rhineland Study.

Another limitation of our study is that the accuracy of self-reported medication use may be culture-dependent, particularly for drugs vulnerable to stigma. In addition, our study population could represent a "healthier" population, as health status could influence drug metabolism, which could limit the generalizability of the results. Although frail older adults are less likely to participate in our study, our population does not appear to be healthier than the general German population, as, for example, the prevalence of hypertension and polypharmacy is comparable.[40,41] Furthermore, we used an untargeted metabolomics panel, which cannot detect all marketed drugs. Nevertheless, we were able to analyse concordances of a variety of commonly used drugs from different drug classes. Although an untargeted metabolomic approach does not allow quantification but rather focuses on simultaneous detection of different metabolites, we do not consider the use of an untargeted approach to be critical, as we only assessed drug use (metabolite detected) and nonuse (metabolite not detected), and were not interested in actual concentrations. Although, to our knowledge, this is the largest study on concordance rates of self-reported medication use and measured metabolites in plasma, for some drugs the number of individuals using the respective drug was still small, resulting in wide confidence intervals. A small number of users may be the reason why we found no indications of age- or sex-related effects on concordances. Another limitation could be that we did not adapt the blood sampling and storage to the individual characteristics of the specific drug metabolite. To ensure that included drug metabolites were suitable for detection, we checked the pharmacokinetic properties of the drugs a priori. Finally, variability in longevity and detection of drug metabolites may depend on age, health status and genetic, metabolic and microbiome variations.[42–45]

Our study shows that in our general population self-reported medication intake is a reliable and accurate method to assess medication intake, even for drugs considered to be prone to stigmatization.

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COMPETING INTERESTS

The authors report no competing interests in this work.

CONTRIBUTORS

N.A. conceptualization, methodology, formal analysis, writing- original draft, visualization. J.C.S. conceptualization, methodology, writing – review and editing, supervision. M.M.B.B. conceptualization, methodology, resources, data curation, writing – review and editing, supervision, funding acquisition. F.M.deV. conceptualization, methodology, data curation, writing – review and editing, visualization, supervision, project administration.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Nersi Alaeddin https://orcid.org/0000-0003-1960-9812
Julia C. Stingl https://orcid.org/0000-0002-1566-8156
Monique M. B. Breteler https://orcid.org/0000-0002-0626-9305
Folgerdiena M. de Vries https://orcid.org/0000-0002-8621-1532

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APPENDIX A

TABLE A1 Drugs and corresponding metabolites in the metabolomics panel per drug class

Drug class	Drug	Measured metabolite(s)
Analgesic/anesthetic	Acetaminophen	(a) 2-acetamidophenol sulphate (b) 2-hydroxyacetaminophen sulphate (c) 2-methoxyacetaminophen glucuronide (d) 2-methoxyacetaminophen sulphate (e) 3-(cystein-*S*-yl) acetaminophen (f) 3-(methylthio) acetaminophen sulphate (g) 3-(*N*-acetyl-L-cystein-*S*-yl) acetaminophen (h) 4-acetamidophenol (i) 4-acetamidophenylglucuronide (j) 4-acetaminophen sulphate
	Celecoxib	Celecoxib
	Ibuprofen	(a) Ibuprofen (b) 2-hydroxyibuprofen (c) Carboxyibuprofen (d) Carboxyibuprofen glucuronide (e) Ibuprofen acyl glucuronide
	Naproxen	(a) Naproxen (b) Desmethylnaproxen (c) Desmethylnaproxen sulfate
	Tramadol	(a) Tramadol (b) *N*-desmethyl tramadol (c) *O*-desmethyltramadol (d) *O*-desmethyltramadol glucuronide
Antibiotic	Doxycycline	Doxycycline
	Fluconazole	Fluconazole
	Ofloxacin	Ofloxacin
Anti-inflammatory	*N*-acetyl sulfapyridine	*N*-acetyl sulfapyridine
Antimalarial	Quinine	Quinine
Immunosuppressant	Mycophenolic acid	(a) Mycophenolic acid (b) Mycophenolic acid glucuronide
Antihypertensive	Enalapril	Enalapril
	Hydrochlorothiazide	Hydrochlorothiazide
	Metoprolol	(a) Metoprolol (b) Metoprolol acid
	Candesartan	Candesartan
	Olmesartan	Olmesartan
	Valsartan	Valsartan
Antiarrhythmic	Verapamil	Verapamil
Ulcer therapeutic	Omeprazole	Omeprazole
	Pantoprazole	Pantoprazole
	Ranitidine	(a) Ranitidine (b) Ranitidine *N*-oxide
Uricostatic	Allopurinol	(a) Allopurinol (b) Oxypurinol
Antihyperglycemic	Metformin	Metformin
	Sitagliptin	Sitagliptin
Antiepileptic	Carbamazepine	(a) Carbamazepine (b) Carbamazepine 10,11-epoxide (c) Carbamazepine glucuronide

TABLE A1 (Continued)

Drug class	Drug	Measured metabolite(s)
	Gabapentin	Gabapentin
	Lamotrigine	Lamotrigine
	Levetiracetam	Levetiracetam
	Pregabalin	Pregabalin
	Topiramate	Topiramate
	Valproate	(a) Valproate (b) 2-propyl-4-pentenoate (4-ene-valproate) (c) 3-hydroxyvalproate
Antidepressant	Citalopram	(a) Citalopram-*N*-oxide (b) Citalopram propionate (c) Desmethylcitalopram (d) Escitalopram
	Escitalopram	(a) Citalopram-*N*-oxide (b) Citalopram propionate (c) Desmethylcitalopram (d) Escitalopram
	Duloxetine	4-hydroxy duloxetine glucuronide
	Fluoxetine	Fluoxetine
	Venlafaxine	(a) Venlafaxine (b) *O*-desmethylvenlafaxine
Antipsychotic	Quetiapine	(a) Quetiapine (b) *N*-desalkylquetiapine
Analgesic/antiemetic	Tetrahydrocannabinol	(a) Tetrahydrocannabinol carboxylic acid (b) Tetrahydrocannabinol carboxylic acid glucuronide
Antihistamine	Cetirizine	Cetirizine
	Diphenhydramine	Diphenhydramine
	Fexofenadine	Fexofenadine
Antitussive	Dextromethorphan	Dextromethorphan
Topic agent	Hydroquinone sulphate	Hydroquinone sulphate
	Salicylate	Salicylate

TABLE A2 Retention index and mass-to-charge ratio (*m*/*z*) for analysed drugs

Drug	Measured metabolite(s)	Retention index	Mass-to-charge ratio (*m*/*z*)
Enalapril	Enalapril	900	377.2071
Hydrochlorothiazide	Hydrochlorothiazide	2046	295.9572
Metoprolol	(a) Metoprolol	(a) 760	(a) 268.1907
	(b) Metoprolol acid	(b) 2950	(b) 268.1543
Candesartan	Candesartan	3436	439.1524
Olmesartan	Olmesartan	3747	445.1994
Valsartan	Valsartan	4228	434.2198
Allopurinol	(a) Allopurinol	(a) 1530	(a) 135.0312
	(b) Oxypurinol	(b) 1656	(b) 151.0262
Metformin	Metformin	2817	130.1087
Sitagliptin	Sitagliptin	4485	468.1112
Gabapentin	Gabapentin	2407.4	170.1187
Citalopram	(a) Citalopram-*N*-oxide	(a) 905	(a) 341.166
	(b) Citalopram propionate	(b) 4400	(b) 310.0885
	(c) Desmethylcitalopram	(c) 880	(c) 311.1554
	(d) Escitalopram	(d) 908	(d) 325.1711
Escitalopram	(a) Citalopram-*N*-oxide	(a) 905	(a) 341.166
	(b) Citalopram propionate	(b) 4400	(b) 310.0885
	(c) Desmethylcitalopram	(c) 880	(c) 311.1554
	(d) Escitalopram	(d) 908	(d) 325.1711
Fluoxetine	Fluoxetine	1025	310.1413
Venlafaxine	(a) Venlafaxine	(a) 848	(a) 278.2115
	(b) *O*-desmethylvenlafaxine	(b) 660	(b) 264.1958
Quetiapine	(a) Quetiapine	(a) 874	(a) 384.174
	(b) *N*-desalkylquetiapine	(b) 874	(b) 296.1958

TABLE A3 Top 50 drugs used regularly in the Rhineland Study

Rank	Drug	Rank	Drug
1	Levothyroxine	26	Losartan
2	Acetylsalicylic acid	27	**Venlafaxine**
3	**Hydrochlorothiazide**	28	**Citalopram**
4	Bisoprolol	29	Ezetimibe
5	**Candesartan**	30	**Sitagliptin**
6	Ramipril	31	**Enalapril**
7	Atorvastatin	32	Rivaroxaban
8	Amlodipine	33	Clopidogrel
9	Pantoprazole	34	Desogestrel
10	Simvastatin	35	Prednisolone
11	Estradiol	36	Omeprazole
12	Ethinylestradiol	37	**Olmesartan**
13	**Metformin**	38	**Escitalopram**
14	**Metoprolol**	39	Phenprocoumon
15	**Valsartan**	40	Amitriptyline
16	Formoterol	41	Levonorgestrel
17	Estriol	42	Telmisartan
18	**Allopurinol**	43	Nebivolol
19	Tamsulosin	44	Mirtazapine
20	Budesonide	45	Irbesartan
21	Progesterone	46	Lisinopril
22	Latanoprost	47	Lercanidipine
23	Beclomethasone	48	Fluticasone
24	Torasemide	49	Ibuprofen
25	Dienogest	50	Levodopa

Note. Analysed drugs in bold

TABLE A4 Concordance between self-reported drug use and measured metabolites with kappa (κ) values (95% CI) stratified for sex

		Women (n = 2459)						Men (n = 1927)					
Drug class	**Drug**	**Regular users**	**TP**	**FP**	**TN**	**FN**	**Cohen's kappa (κ) (95% CI)**	**Regular users**	**TP**	**FP**	**TN**	**FN**	**Cohen's kappa (κ) (95% CI)**
Antihypertensive	Hydrochlorothiazide	183	90	93	2271	5	0.63 (0.56–0.7)	172	78	94	1752	3	0.59 (0.52–0.67)
	Metoprolol	63	56	7	2386	10	**0.86 (0.80–0.93)**	38	36	2	1879	10	**0.85 (0.77–0.94)**
	Candesartan	138	133	5	2319	2	**0.97 (0.95–0.99)**	141	136	5	1784	2	**0.97 (0.95–0.99)**
	Olmesartan	13	11	2	2446	0	**0.92 (0.8–1.00)**	25	24	1	1902	0	**0.98 (0.94–1.00)**
	Valsartan	53	50	3	2403	3	**0.94 (0.90–0.99)**	45	44	1	1881	1	**0.98 (0.95–1.00)**
Uricostatic	Allopurinol	15	15	0	2430	14	0.68 (0.52–0.83)	77	70	7	1841	9	**0.89 (0.84–0.95)**
Antihyperglycemic	Metformin	39	32	7	2419	1	**0.89 (0.81–0.96)**	70	57	13	1855	2	**0.88 (0.82–0.94)**
	Sitagliptin	15	11	4	2444	0	**0.85 (0.70–0.99)**	31	20	11	1896	0	0.78 (0.66–0.91)
Antiepileptic	Gabapentin	5	5	0	2454	0	**1.00 (1.00–1.00)**	14	9	5	1912	1	0.75 (0.55–0.94)
Antidepressant	(Es-)citalopram	63	62	1	2388	8	**0.93 (0.89–0.98)**	27	24	3	1895	5	**0.86 (0.76–0.95)**
	Fluoxetine	16	16	0	2439	4	**0.89 (0.78–1.00)**	3	3	0	1924	0	**1.00 (1.00–1.00)**
	Venlafaxine	37	35	2	2420	2	**0.95 (0.89–1.00)**	12	12	0	1914	1	**0.96 (0.88–1.00)**
Antipsychotic	Quetiapine	13	13	0	2444	2	**0.93 (0.83–1.00)**	3	3	0	1924	0	**1.00 (1.00–1.00)**

Note: Kappa values in bold show an almost perfect agreement (κ > 0.8).

Abbreviations: CI, confidence interval; FN, false negative (metabolite detected but no self-reported use); FP, false positive (metabolite not detected but self-reported use); TN, true negative (metabolite not detected and no self-reported use); TP, true positive (metabolite detected and self-reported use).

TABLE A5 Concordance between self-reported drug use and measured metabolites with kappa (κ) values (95%CI) stratified for age groups

		< 65 years (n = 3216)						≥ 65 years (n = 1170)					
Drug class	**Drug**	**Regular users**	**TP**	**FP**	**TN**	**FN**	**Cohen's kappa (κ) (95% CI)**	**Regular users**	**TP**	**FP**	**TN**	**FN**	**Cohen's kappa (κ) (95% CI)**
Antihypertensive	Hydrochlorothiazide	139	73	66	3075	2	0.67 (0.60–0.75)	216	95	121	948	6	0.55 (0.48–0.61)
	Metoprolol	41	35	6	3164	11	0.80 (0.71–0.89)	60	57	3	1101	9	**0.90 (0.84–0.96)**
	Candesartan	113	106	7	3100	3	**0.95 (0.92–0.98)**	166	163	3	1003	1	**0.99 (0.97–1.00)**
	Olmesartan	14	11	3	3202	0	**0.88 (0.74–1.00)**	24	24	0	1146	0	**1.00 (1.00–1.00)**
	Valsartan	38	35	3	3177	1	**0.95 (0.89–1.00)**	60	59	1	1107	3	**0.97 (0.93–1.00)**
Uricostatic	Allopurinol	37	32	5	3165	14	0.77 (0.67–0.87)	55	53	2	1106	9	**0.90 (0.84–0.96)**
Antihyperglycemic	Metformin	41	33	8	3172	3	**0.86 (0.77–0.94)**	68	56	12	1102	0	**0.90 (0.84–0.96)**
	Sitagliptin	17	11	6	3199	0	0.78 (0.62–0.95)	29	20	9	1141	0	**0.81 (0.69–0.93)**
Antiepileptic	Gabapentin	8	4	4	3207	1	0.61 (0.30–0.93)	11	10	1	1159	0	**0.95 (0.86–1.00)**
Antidepressant	(Es-)citalopram	62	59	3	3143	11	**0.89 (0.84–0.95)**	28	27	1	1140	2	**0.95 (0.89–1.00)**
	Fluoxetine	14	14	0	3199	3	**0.90 (0.79–1.00)**	5	5	0	1164	1	**0.91 (0.73–1.00)**
	Venlafaxine	33	32	1	3181	2	**0.95 (0.90–1.00)**	16	15	1	1153	1	**0.94 (0.85–1.00)**
Antipsychotic	Quetiapine	14	14	0	3200	2	**0.93 (0.84–1.00)**	2	2	0	1168	0	**1.00 (1.00–1.00)**

Note: Kappa values in bold show an almost perfect agreement ($\kappa > 0.8$).

Abbreviations: CI, confidence interval; FN, false negative (metabolite detected but no self-reported use); FP, false positive (metabolite not detected but self-reported use); TN, true negative (metabolite not detected and no self-reported use); TP, true positive (metabolite detected and self-reported use).